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DESCRIPTION OF AN INVENTION
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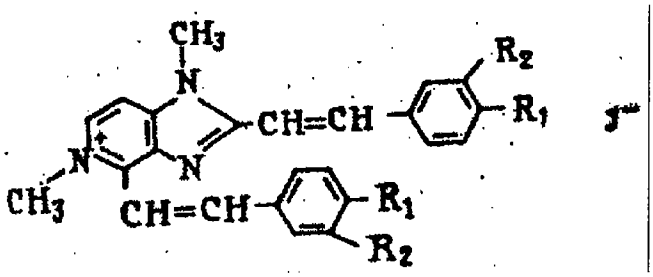
(54) 2,4-DISTYRYL DERIVATIVES OF IMIDAZO[4,5-*c*]PYRIDINIUM EXHIBITING BACTERIOSTATIC AND FUNGISTATIC ACTIVITY

(57) 2,4-Distyryl derivatives of imidazo[4,5-*c*]pyridinium having the general formula



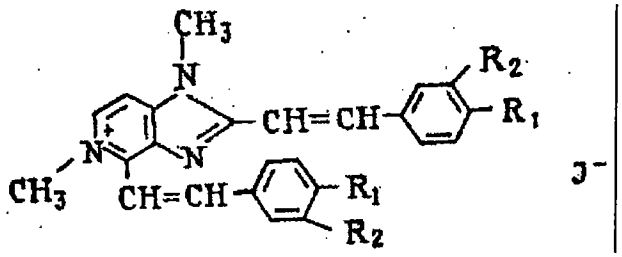
where a) $R_1 = N(CH_3)_2$ and $R_2 = H$, and b) $R_1 = R_2 = OCH_3$,
which exhibit bacteriostatic and fungistatic activity.

The invention relates to new chemical compounds of the imidazopyridine series, specifically to 2,4-distyryl derivatives of imidazo[4,5-*c*]-pyridinium, which exhibit bacteriostatic and fungistatic activity and can be used in the chemical-pharmaceutical industry.

5-Dodecyl-1-methylimidazo[4,5-*c*]-pyridinium bromide, which exhibits antimicrobial and fungistatic activity, has been described in the patent literature. However, it has high toxicity (LD_{50} = 13 mg/kg).

The object of the invention is to expand the toolkit for acting on the living organism.

The stated object is attained by the described 2,4-distyryl derivatives of imidazo[4,5-c]-pyridinium having the general formula:



where a) $R_1 = N(CH_3)_2$ and $R_2 = H$, and b) $R_1 = R_2 = OCH_3$,
which are obtained by reacting 1,2,4,5-tetramethylimidazo[4,5-*c*]pyridinium iodide with an excess of the corresponding aromatic aldehyde in the presence of piperidine as a catalyst.

Example 1. 2,4-Di-(*n*-N′,N′-dimethylaminostyryl)-1,5-dimethylimidazo[4,5-*c*]pyridinium iodide (1a).

A quantity of 0.1 g (3.3×10^{-4} mol) of 1,2,4,5-tetramethylimidazo[4,5-*c*]pyridinium iodide and 0.2 g (13.2×10^{-4} mol) of *n*-N,N-dimethylaminobenzaldehyde is dissolved, while being heated in 5 mL of *n*-butanol, 0.24 mL (2.4×10^{-4} mol) of piperidine is added, and [the resulting mixture] is boiled on an oil bath at a temperature of 135–145°C for 3.5 hr. After cooling, the cherry-colored precipitate is filtered off and washed with ether; the yield is 0.072 g (38.6%), and m.p. is 250°C with decomposition (*n*-butanol).

EPR spectrum, δ, ppm (CF_3COOH): 3.02 [*c*, $-(CH_3)_2$]; 3.92 [*c*, 1(5)–CH_3]; 4.12 [*c*, 5(1)–CH_3]; 7.30–7.55 (*m*, $-C_6H_4-$ and –CH=CH–); 7.72 [*d*, 7(6)–H, I = 6.5 Hz]; 8.43 [*d*, 6(7)–H, I = 6.5 Hz].

Found: C 59.7%; H 6.0 %; N 22.3%.

$C_{28}H_{32}N_5I$.

Calculated: C 59.5%; H 5.7%; N 22.4%.

Example 2. 2,4-Di-(3,4-dimethoxystyryl)-1,5-dimethylimidazo-[4,5-*c*]-pyridinium iodide (1b).

[This compound] is obtained, by analogy with Example 1, by proceeding from 0.1 g (3.3×10^{-4} mol) of 1,2,4,5-tetramethylimidazo[4,5-*c*]pyridinium iodide and 0.25 g (1.5×10^{-4} mol) of 3,4-dimethoxybenzaldehyde; yield is 0.15 g (75.8%) of a substance of light-brown color, and m.p. is 175–176°C (*n*-butanol).

EPR spectrum (CF_3COOH, δ, ppm): 3.60 (*c*, 2,5-OCH_3); 3.89 [*c*, 1(5)-CH_3]; 4.09 [*c*, 5(1)–CH_3]; 6.6–7.23 (*m*, $-C_6H_3-$ and –CH=CH–); 7.69 [*d*, 7(6)–H, I = 6.5 Hz]; 8.33 (*d*, 6(7)–H, I = 6.5 Hz).

Found: C 55.8%; H 5.2%; N 20.9%.

$C_{28}H_{30}N_3IO_4$.

Calculated: C 56.1%; H 5.0%; N 21.2%.

The bacteriostatic activity of the compounds was studied by the method of doubling dilutions on a liquid medium. Hottinger broth (*p*H 7.2–7.4) was used to culture the bacteria. The microbial load for the bacteria was 5×10^5 cells of an 18-hr agar culture in 1 mL of medium. The highest of the tested concentrations was 200 μg/mL.

Sabouraud's medium (*p*H 6.0–6.8) was used to grow the fungi. The load was 500,000 reproductive bodies per milliliter. The highest of the tested concentrations was 200 μg/mL. The antimicrobial activity of the compounds [was determined] from the minimum bacteriostatic or mycostatic concentration of chemical compounds, expressed in μg/mL.

The test results for activity and toxicity are presented in the table.

Thus, 2,4-distyryl derivatives of imidazo[4,5-*c*]-pyridinium having general formula 1 possess a broader spectrum of bacteriostatic and fungistatic activity than does 5-dodecyl-1-methylimidazo[4,5-*c*]pyridinium bromide, and also are less toxic compounds.

Test Results for Antimicrobial and Fungistatic Activity
(the minimum bacteriostatic and mycostatic concentrations are specified in μg/mL)

Strain of microorganisms and fungi	**2,4-Distyryl derivatives of imidazo[4,5-c]-pyridinium**	
	1a	**1b**
Staphylococcus aureus 209 P	100	>200
Escherichia coli 675	200	>200
Shigella Flexneri	50	200
Bacillus anthracoides 1312	6.25	200
Microsporum lanosum 257	50	200
Trichophyton mentag. IMI 124768	50	200
Aspergillus niger BKMF-1119	200	>200
Toxicity, LD_{50} (mg/kg)	44.7 ± 6.05	48.7 ± 2.67

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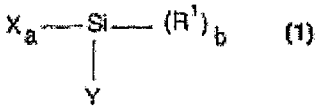
(54) Title: Silanes and Polyorganosiloxanes with boronate function(s)



(1)

(2)

(57) Abstract

The invention concerns silanes of formula (1) wherein Y is a boronate group of formula (2), wherein: c and d are integers ranging from 0 to 18; c + d = 0 to 18; e is selected between 0 and 1; Z is a divalent heterocarbon group comprising one or several heteroatoms such as O, S, and/or N. The invention also concerns the corresponding polyorganosiloxanes, the methods for preparing them and compositions containing them.

Silanes and Polyorganosiloxanes with boronate function(s)

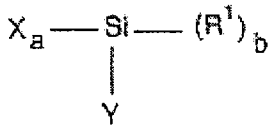
The present invention concerns novel functionalized silanes and polyorganosiloxanes, as well as compositions comprising a polyorganosiloxane of this type as a base polymer, capable of crosslinking into an elastomer through exposure to ambient air humidity without the aid of a crosslinking catalyst.

It also concerns the preparation processes of these silanes and polyorganosiloxanes.

Single-component silicone compositions (that is, in the form of a single package) capable of hardening or crosslinking via polycondensation reaction through exposure to ambient air humidity at room temperature are well known to those skilled in the art and are described in numerous patent documents. In this context one generally utilizes a tin base catalyst capable of generating degradation reactions of the elastomer formed during age-hardening of the latter.

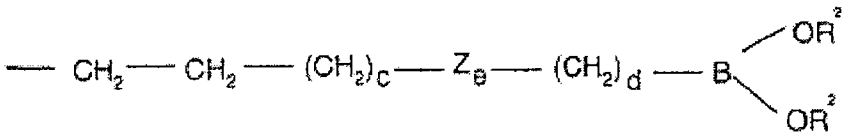
The main objective of the invention is to propose a polyorganosiloxane-based silicone composition for thin- and thick-film coating that is storage-stable in the absence of humidity and hardenable at room-temperature without the aid of a crosslinking catalyst.

A first object of the invention concerns the silicones that are used to prepare the polyorganosiloxanes according to the invention and which correspond to the formula (1):



wherein:

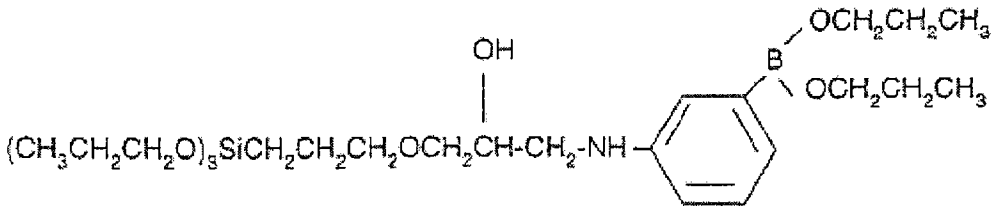
- R^1 is selected from a monovalent hydrocarbonate group, possibly substituted by halogen atoms,
- X is a hydrolysable group,
- a is selected between 1, 2 and 3,
- b is selected between 0, 1 and 2,
- a + b = 3
- Y is a boronate group of formula (2)



wherein:

- c and d are integers ranging from 0 to 18
- c + d = 0 to 18
- e is selected between 0 and 1,
- Z is a divalent heterocarbon group comprising one or several heteroatoms such as O, S and/or N; well suited are: -O-, -CO-, -COO-, phenylene, -NR'- with R' = H or straight-chain or branched-chain C1-C4, -S- alkyl
- R^2 groupings, which can be identical or different, are selected from hydrogen atoms, straight or branched-chain C1-C20 alkyl radicals, preferably C1-C6, C5-C8 cycloalkyls, C6-C12 aryls, or with boron and oxygen atoms can form a heterocycle consisting of 5 to 8 elements (heterocycle atoms), preferably 5 to 6; the carbons may possibly be substituted,

being excluded the silane of formula



This particular silane, excluded by disclaimer, was disclosed by M. Glad et al., J. Chromato., 1985, 347: 11-23. It is used in the field of chromatography to produce a polysiloxane coating on porous silica to enable molecular imprinting or enzyme fixation.

Preferably, in formula (2), one will select:

either:
- c + d = 0 or 1
- e = 0
- R^2 = straight- or branched-chain C1-C4 and/or H alkyl groupings,

or:
- c = 0 or 1
- d = 0
- e = 1
- Z is a phenyl group
- R^2 = straight- or branched-chain C1-C4 and/or H alkyl groupings.

Preferably, in formula (1), the radicals R^1, identical or different, are C1-C10 hydrocarbon radicals, substituted or unsubstituted by halogen atoms.

These radicals notably comprise:

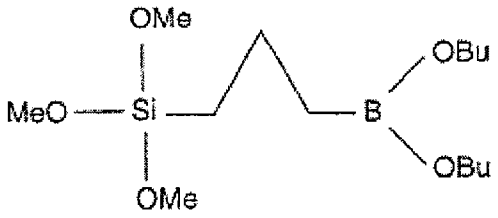
- C1-C10 alkyl and halogen alkyl radicals, such as the radicals: methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, ethyl-2 hexyl, octyl, decyl, trifluoro-3,3,3 propyl, trifluoro-4,4,4 butyl, pentafluoro-4,4,4, 3,3 butyl,
- C3-C10 cycloalkyls and halogenocycloalkyls, preferably C5-C8, such as the radicals: cyclopentyl, cyclohexyl, methylcyclohexyl, propylcyclohexyl, difluoro-2,3 cyclobutyl, difluoro-3,4 methyl-5 cycloheptyl,
- C2-C4 alkenyl radicals, such as the radicals: vinyl, allyl, butene-2-yl,
- mononuclear C6-C10 aryl and halogen aryl radicals, such as the radicals: phenyl, tolyl, xylyl, chlorophenyl, dichlorophenyl, trichlorophenyl.

The preferred radicals are methyl, phenyl, vinyl and trifluoro-3,3,3.

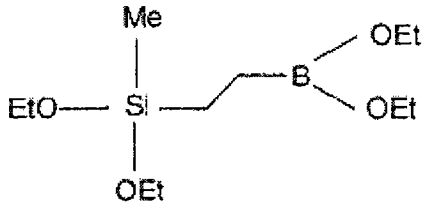
The hydrolyzable X radicals, identical or different, are more specifically selected from a halogen atom (preferably chlorine) and among N-substituted amino radicals: N-substituted amido, N,N di-substituted aminoxy, cetiminoxy, aldimonoxy, alkoxy, alkoxy alkylene-oxy, enoxy, acyloxy. For more details concerning the X radicals that can be used, those skilled in the art may refer to EP-B1-430 826.

Methoxy, ethoxy and acetoxy radicals are particularly suitable.

As preferred silanes, one may cite the following:



(A)



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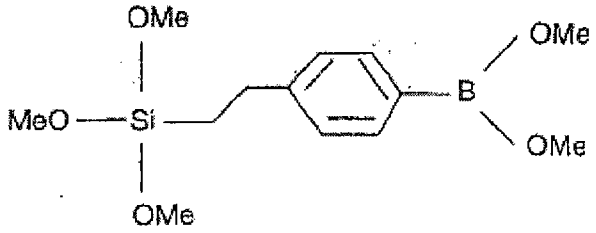

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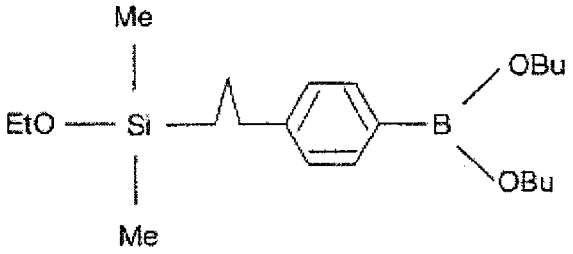
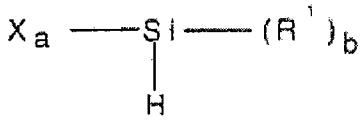


(D)

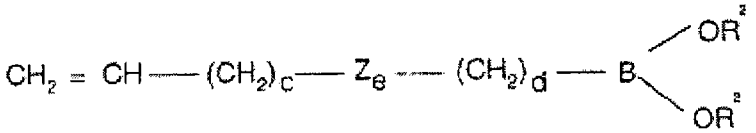
The silanes can be prepared via hydrosilylation reaction between:

- a silane of formula (3)



wherein: X, a, R^1 and b have the same meanings as above, and

- an unsaturated alkyl dialkoxy borane of formula (4)



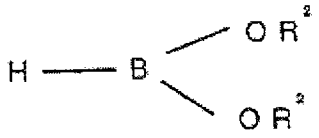
wherein:

- c and d are integers ranging from 0 to 18
- c + d is at the most equal to 18
- R^2, Z and e have the same meanings as above.

This reaction is carried out in the presence of a conventional hydrosilylation catalyst such as rhodium, platinum, in the presence possibly of an inert solvent such as toluene or cyclohexane, at a temperature ranging between room temperature and 120°C.

Preferably, the unsaturated alkyl dialkoxy borane is such that c = 0 or 1, e = d = 0.

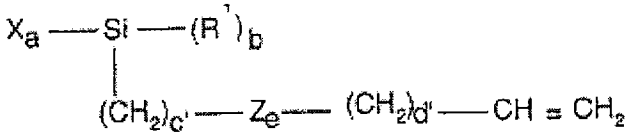
Certain silanes can also be prepared by hydroboration reaction by causing to react together:



(5),

wherein R_2 is as above, and:

(6)



wherein:

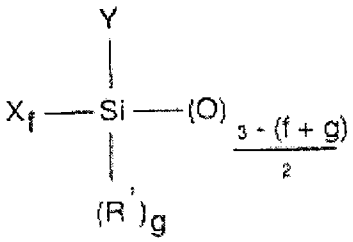
- c = 2 to 18
- d' = 0 to 16
- c' + d' = 2 to 18
- R^1, b, X, a, Z, e have the same meanings as above,
- with the possibility, when e = 0, that c' = 0 and d' = 0 or 1 (c' + d' = 0 or 1).

This reaction is carried out with or without catalyst, possibly in the presence of a solvent like cyclohexane, at a temperature ranging from -50°C to +100°C.

As preferred examples, functionalized silanes according to the invention can be prepared through hydrosilylation of a vinyl dialkoxy borane (c = 0, formula (4)) or an allyl dialkoxy borane (c = 1, formula (4)), or through hydroboration of a vinyl silane (c' = d' = e = 0, formula (6)), or an allyl silane (c' = 1, e = d' = 0, formula (6)). One may further specify that these alkoxy groupings are preferably methoxy, ethoxy, propyloxy, butyloxy, pentyloxy or hexyloxy groupings. Allyl dibutoxy borane, also known as butyl allyl boronate, will be mentioned as a suitable example, where in formula (4) c = 1, d = e = 0, R^2 = butyl.

The functionalized silanes of formula (1) can be used as such, notably as adherence promoters in elastomeric compositions or as a crosslinking agent in crosslinking polycondensation reactions for silicone compositions (preferably in that case silanes (1) where a = 2 or 3).

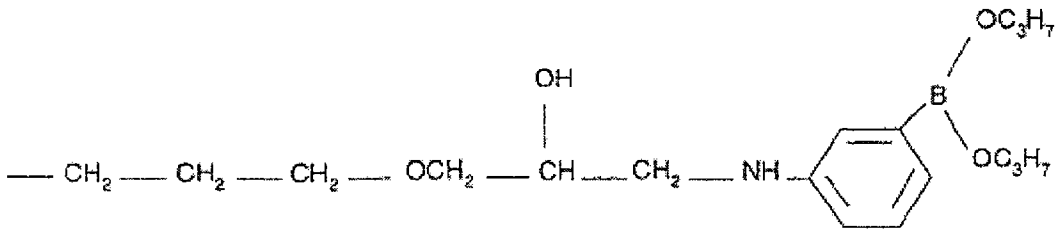
The second object of the invention also concerns polyfunctional polyorganosiloxanes comprising per molecule at least one unit corresponding to the general formula (7):



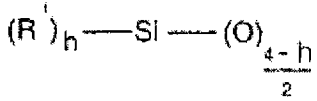
wherein:

- R^1, X and Y have the same meaning as in formula (1),
- f is selected from among 0, 1 or 2,
- g is selected from among 0, 1 or 2,
- f + g is at most equal to 2,

being excluded the polyorganosiloxane in which f + g = 0 and Y is such that:



The polyfunctional polyorganosiloxane can have, on the one hand, at least one unit (7) taken without its disclaimer and, on the other, other siloxyl units corresponding to the formula (8):



wherein:

- R^1 has the same meaning as formula (1)
- h is selected from among 0, 1, 2, and 3.

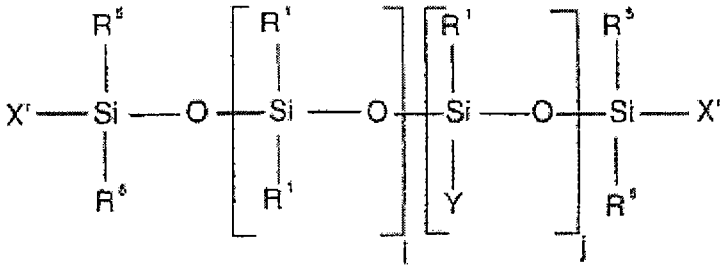
Preferably, R^1 is selected from the radicals: methyl, phenyl and vinyl, at least 80% by number of the R1 radicals being methyl.

The polyorganosiloxanes according to the invention can therefore have a straight-chain, cyclic or branched-chain structure.

Preferred are straight-chain or cyclic polyorganosiloxanes having per molecule at least one unit of formula (7) where f + g is different from zero, and possibly at least one unit of formula (8) where h is equal to 2 or 3.

Such straight-chain or cyclic polymers can possibly include T units of formula (7) where f + g = 0 and/or T units of formula (8) where h = 1 and/or possibly Q units of formula (8) where h = 0 in a proportion of at least 2% (these % expressing the number of T and/or Q units per 100 atoms of silicon).

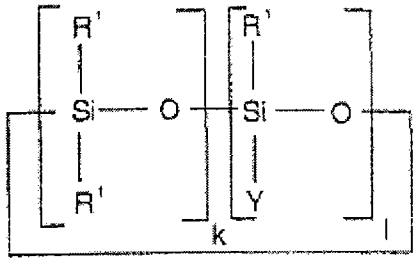
The present invention notably concerns the polyfunctional polyorganosiloxanes of formula (9):



wherein:

- R^1, X and Y have the same meaning as in formula (1) [handwritten: without its disclaimer],
- X' is selected from among the radicals Y, R^1, hydroxyl and hydrogen atom,
- the radicals R^5, identical or different, are selected from the radicals R^1 and X
- i is an integer between 0 and 1000,
- j is an integer between 0 and 50,
- if j = 0, at least 1 of the radicals X^1 is Y.

The invention also concerns the polyorganosiloxanes of formula (10).



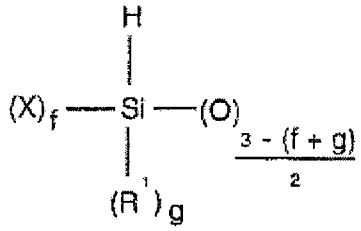
wherein:

- R^1 and Y have the same meaning as in formula (1) [handwritten: without its disclaimer],
- k is an integer between 0 and 9, inclusive,
- l is an integer between 1 and 9, inclusive,
- k + l is between 3 and 10, inclusive.

These polyfunctional polyorganosiloxanes can be prepared according to different processes.

A first process consists in bringing about a hydrosilylation reaction between:

- a polyorganosiloxane having per molecule at least one unit of formula (11):

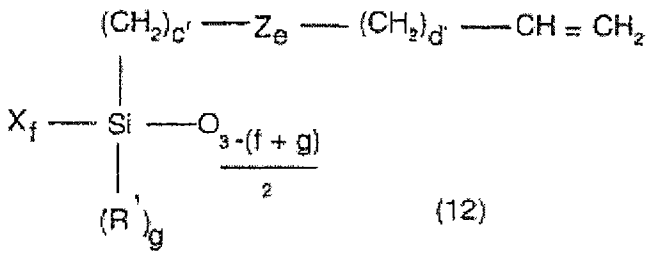


wherein X, f, R^1, g have the same meanings as in formula (7), without its disclaimer, and

- an unsaturated alky dialkoxy borane of formula (4), above.

Preferably, the compound of formula (4) is such that c = 0 or 1 and e = d = 0.

Certain polyorganosiloxanes can be prepared via hydroboration reaction between the compound of formula (5), and:



(12)

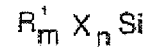
wherein c' = 2 to 18

d' = 0 to 16

c' + d' = 2 to 18

formulas (12) and (12') wherein X, f, R^1, g and Z have the same meanings as above, with the possibility, when e = 0, that c' = 0 and d' = 0 or 1 (c' + d' = 0 or 1).

Yet another process consists in producing the polyorganosiloxane via hydrolysis and/or redistribution reactions from a functionalized silane of formula (1) according to the invention with a cyclic or branched-chain polysiloxane comprising units of formula (8) wherein h = 2 or 3, or with a hydrolyzable silane corresponding to formula (13):



wherein:

- R^1 has the same meaning as formula (1),
- m = 2 or 3,

- $m + n = 4$,
- X as described in formula (1).

In the case where polycondensation is stopped by neutralization, one obtains a reaction mixture comprising cyclic polymers of formula (10) and/or branched polymers of formula (9) blocked at each of their ends by a hydroxyl group or by the unit:

$R^1_2YSiO_{0,5}$ if at the start one additionally utilizes the silane R^1_2YSiCl or the corresponding disiloxane.

One can also stop the polycondensation by adding, at the end of reaction, an organosilicon compound susceptible to reacting with the terminal hydroxyls of the formula (9) polymer formed, whereby this organosilicon compound corresponds to the formulas:

R^1_3SiCl, $R^1_3SiNHSiR^1_3$ and $R^1_3SiOSiR^1_3$.

Hydrolysis duration can vary between a few seconds and several hours.

After hydrolysis, the aqueous phase is separated from the siloxane phase by any suitable physical means, usually by decantation and/or extraction via an organic solvent like isopropyl ether or toluene.

In the presence of humidity, the polyfunctional polyorganosiloxanes of the invention crosslink to form very UV- and temperature-stable boroxines. They can also be placed in aqueous solution in the form of stable boronic acid, crosslinkable in boroxine via elimination of water.

These polyorganosiloxanes can be utilized pure to form, for example, coatings after crosslinking, in the absence of a catalyst, in the presence of humidity or by elimination of water, as required.

They are particularly usable as base diorganopolysiloxane polymers, within a silicone compound crosslinkable into an elastomer, in the absence of a catalyst, through exposure to atmospheric humidity or through elimination of water, depending on the case.

These silicone compounds can be single-packaged and are storage-stable.

In a third object, the invention thus concerns an organopolysiloxane compound, storage-stable in the absence of humidity and capable of crosslinking through exposure to humidity in the absence of a crosslinking catalyst, comprising:

(A) – 100 parts by weight of at least one polymer of formula (7) without its disclaimer, possibly with units (8), or of formula (9) or (10), according to the invention

(B) – 0 to 250 parts by weight of a mineral filler.

It therefore also concerns an aqueous organopolysiloxane compound, storage-stable in the absence of humidity and capable of crosslinking through elimination of water in the absence of a crosslinking catalyst, comprising:

(A) – 100 parts by weight of at least one polymer, a polymer of formula (7) without its disclaimer, possibly with units (8), or of formula (9) or (10), according to the invention

(B) – 0 to 250 parts by weight of a mineral filler.

(C) – 0.5 to 50, preferably 3 to 20, parts by weight of water.

(D)– possibly a non-ionic, anionic, cationic or amphoteric tensioactive agent.

Mineral fillers (B) are used at the rate of 0 to 250 parts, preferably 20 to 200 parts, per 100 parts of polymer (A).

These fillers can be in the form of very finely divided products whose mean particle diameter is less than 0.1 micrometer. These fillers include combustion silica and precipitated silica; their specific BET surface is generally greater than 40 m^2/g.

These fillers can also be in the form of more coarsely divided products whose mean particle diameter is greater than 0.1 micrometer. As examples of such fillers, one may cite milled quartz, diatomaceous silica, calcium carbonate, calcined clay, titanium oxide of the rutyl type, ferrous, zinc, chromium, zirconium, magnesium oxides, various forms of aluminum (hydrated or unhydrated), boron nitride, barium metaborate, glass microbeads; their specific surface is generally less than 30 m^2/g.

These fillers (B) can be surface-modified through treatment with various organosilicon compounds customarily used for this purpose. Accordingly, these organosilicon compounds can be organochlorosilanes, diorganocyclopolysiloxanes, hexorganodisiloxanes, hexorganodisilazanes or diorganocyclopolysiloxanes (French patents FR-A-1 126 884, FR-A-1 136 885, FR-A-1 236 505; English patent GB-A-1 024 234). In the majority of cases, the treated fillers are comprised from 3 to 30% by weight of organosilicon compounds.

The fillers (B) can consist of a mixture of several types of fillers of varying granulometry.

The tensioactive agents (D) possibly utilized can be nonionic tensioactives with an HLB greater than 10, preferably on the order of 10 to 20, anionic, cationic, zwitterionic or amphoteric agents with an HLB greater than 10.

The nonionic tensioactive agents can be selected from alkoxylated fatty acids, polyalkoxylated alkyphenols, polyalkoxylated fatty alcohols, polyalkoxylated or polyglycerolated fatty amides, polyglycerolated alcohols and alphadiols, ethylene oxide-propylene oxide block polymers, as well as alkyl glucosides, alkyl polyglucosides, sucroethers, sucroesters,

sucroglycerides, sorbitan esters, and the ethoxylated compounds of these sugar derivates having an HLB of at least 10.

The anionic tensioactive agents can be selected from alkyl benzene sulfonates, alkyl sulphates, alkyl ether sulfates, alkyl aryl ether sulfates, dialkyl sulfosuccinates, alkyl phosphates, ether phosphates, alkaline metals having an HLB of at least 10.

Among the cationic tensioactive agents one may cite aliphatic or aromatic fatty amines, aliphatic fatty amines, quaternary ammonium derivates, having an HLB of at least 10.

Among the zwitterionic or amphoteric tensioactive agents one may cite betaines and their derivates, sultaines and their derivates, lecithins, imidazoline derivates, glycinates and their derivates, amino propionates, fatty amine oxides having an HLB of at least 10.

The polyorganosiloxanes with boronate functions according to the invention can be utilized in the pure state or in the form of compounds of the type of those cited above, for example in the field of textile conditioning and in the coating of metals, natural stones or various cement-based construction equipment in order to confer nonadherent and/or hydrophobic surface properties to same.

The invention therefore likewise concerns this use as well as the method of treating these different materials or substrates, in which these substrates are coated with the polyorganosiloxanes or compounds according to the invention, in order to confer to these substrates, after crosslinking, adherent and/or hydrophobic properties.

The invention will now be described in greater detail with the aid of non-limiting exemplified embodiments.

Silanes and vinyl silanes are industrial and commercial products. The methods of boron hydride preparation are known. One may cite Jeffers P.M. et al., Inorg. Chem., 1981, 20:1698 for the preparation of $HB(OMe)_2$. The synthesis of allyl dibutoxy borane is described below.

EXAMPLES

Example 1: Synthesis of allyl dibutoxy borane:

Into a 1 liter three-necked flask equipped with a mechanical agitator, an ascendant refrigerant, a 100 ml isobaric funnel, an N_2 valve (all equipment flame-dried under N_2), introduce 0.5 moles of Mg, then freshly distilled BF_3 etherate and 350 ml of anhydrous ether distilled over Na.

Under strong agitation at room temperature, add dropwise a 28.62 g solution of allyl chloride in 50 ml of anhydrous ether. The reaction is triggered through direct introduction of 4 cm^3 (over the 28.60 g) of allyl chloride into the reactor.

The ether rapidly refluxes and, once returned to a reasonable level, is maintained by addition of an allyl chloride solution, under vigorous agitation.

After 1 hour and 30 minutes of addition, the solution is left at room temperature for 2 hours, under vigorous agitation.

Following decantation, the supernatant is transferred under N_2 into a degassed and dry flask for 1 hour.

Add 3 x 200 ml of anhydrous ether over the precipitate under agitation in order to extract the maximum product amount from it. The supernatants formed, the ether is distilled at atmospheric pressure. After transfer under N_2 of the product remaining in the 100 ml flask, the triallyl-borane is distilled at 60°C for 20 minutes.

Yield: 67%.

Into a 100 mg double-neck flask, equipped with magnetic agitation and a refrigerant + valve, all equipment flame-dried under argon, introduce 9 g of freshly distilled triallyl-borane.

Add dropwise an excess of 1-butanol freshly distilled under N_2. The reaction is exothermic. If required, provide water bath cooling at 30-35°C.

Leave one night at room temperature. Then distill the excess of 1-butanol under vacuum at 40 mm Hg (5320 Pa), after that the anticipated product under vacuum at 0.2 to 0.4 mm Hg (26.6 to 53.2 Pa) at 58-62°C; 12.2 g of a colorless liquid is obtained. A slight residue remains. The residue and liquid are collected and redistilled through a 13 cm Vigreux column. The anticipated product (allyl dibutoxy borane) is recovered at 50°C - 52°C under vacuum at 0.1 mmHg (13.3 Pa).

Note: It is possible to not purify the triallyl-borane intermediate and to immediately add butanol.

Example 2: Hydrosilylation of an Si-H oil by the allyl dibutoxy borane obtained in Example 1:

Reagents:

- 7.18 g of polyhydrogenosiloxane oil ($MD_9D'_4M$ [where M = $(CH_3)_3SiO_{1/2}$, D = $(CH_3)_2SiO_{2/2}$ and D' = $H(CH_3)SiO_{2/2}$] having 384 millimoles of SiH units per 100 g of oil and viscosity of 12 mPa·s at 25°C (Brookfield viscometer)
- 6.55 g of allyl dibutoxy borane (0.033 mmoles)
- 10 ppm of Karstedt-type platinum catalyst: solution in the divinyl tetramethyl disiloxane of a platinum compound at approximately 11% by weight of zero-valent platinum liganded by

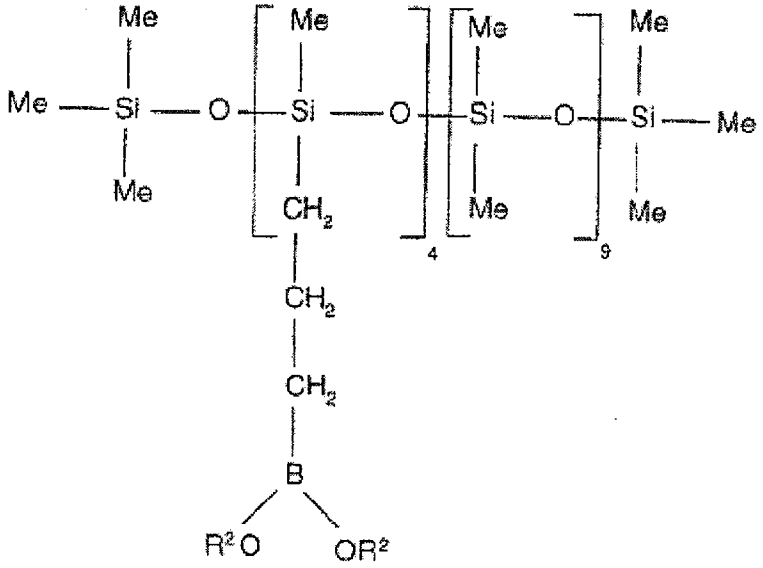
divinyl tetramethyl disiloxane: the quantities of this catalyst are expressed in ppm of Pt metal supplied by the solution in the reaction mixture.

Procedure:

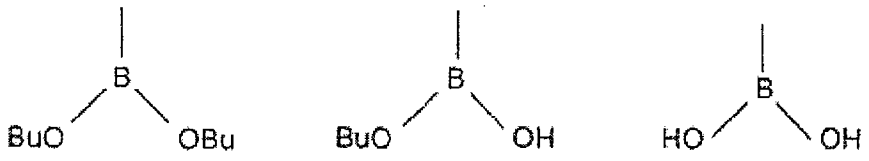
Pour the oil into an isobaric funnel. Introduce the allyl dibutoxy borane and the catalyst into the flask (100 ml three-necked with mechanical agitator). Slowly pour the oil over the alkene. Then heat the reaction medium in the range of 70-75°C for 2 hours.

The IR spectrometer allows reaction progress to be followed by monitoring the disappearance of the SiH band (in the 2100 cm^{-1} region). At the end of reaction, eliminate the reagents that did not react to heating under vacuum (13.3 10^2 Pa.) in the 110-120°C range.

The polyorganosiloxane obtained corresponds to the following formula:



wherein the boronate functions are constituted essentially by a mixture of functions:



a b c

where the a functions are amply in the majority in number.

Example 3: Hydrosilylation of the triethoxysilane by the allyl dibutoxy borane obtained in Example 1:

Product weights:

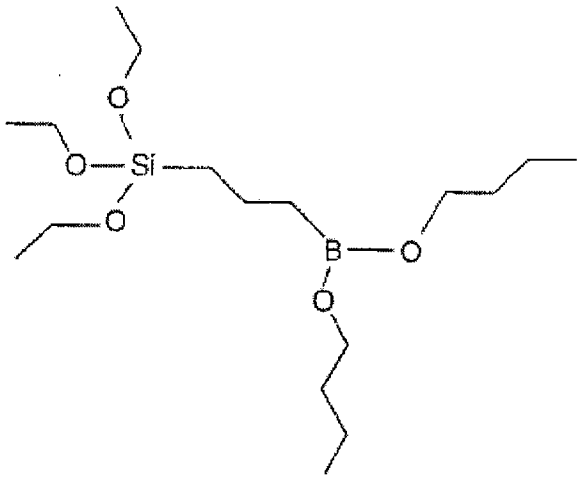
Allyl dibutoxy borane	22.30 g	0.094 mol	1.1 eq.
Triethoxysilane	14.20 g	0.086 mol	1 eq.
Catalyst	0.0009 g		

Procedure:

Into a three-necked flask (dry and under argon), introduce the butyl allyl boronate and Karstedt platinum. Pour the distilled triethoxysilane over this mixture. When finished pouring, heat to 100°C and monitor reaction progress per Si-H dose.

An Si-H dose administered after 24 hours of reaction indicates the reaction has not finished. Re-add catalyst and continue heating. Monitor reaction progress per Si-H dose. At the end of 48 hours, a fourth dose indicates that the transformation rate is 95%.

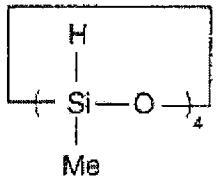
Devolatilize the medium under reduced pressure to eliminate excess butyl allyl boronate. 22 g of product is recovered corresponding to the following formula:



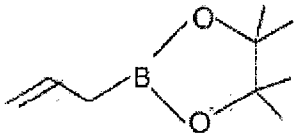
Example 4: Hydrosilylation of allyl pinacol boronate with a cyclic polyorganosiloxane in order to produce 1,3,5,7-tetra-(pinacolboronate)propyl)-1,3,5,7-tetramethyl-cyclotetrasiloxane

Starting compounds:

- cyclic polyorganosiloxane:



- allyl pinacol boronate:



This compound is prepared according to the method described in R.W. Hoffmann et al., Liebigs Ann. Chem. 1986, 1823-1836 or in W.R. Roush et al., J. Am. Chem. Soc. 1986, 108, 3422-3434.

- Karstedt catalyst

Procedure:

Under argon, mix and heat to 60°C allyl pinacol boronate (1.5 ml, 9.1 mmoles) and Karstedt catalyst (1.10^{-4} moles of platinum per mole of allyl pinacol boronate) in toluene (5 ml). After agitation, add the cyclic silane (0.5 ml, 2.1 mmoles). Then heat the solution to 60°C for 4 hours. The solvent is evaporated under reduced pressure and the volatile by-products and excess allyl pinacol boronate extracted through kugelrohr distillation (90% C, 0.2 mm Hg, or 26.6 Pa).

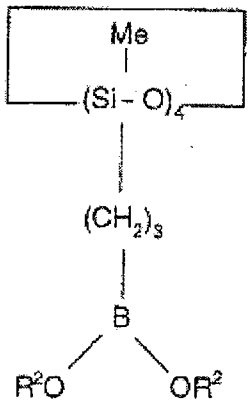
1.31 g of the desired product is obtained.

^{1}H NMR: δ = 0.02 ppm (12H, Si-CH_3), 0.51-0.58 (8H, m, Si-CH_2), 0.74-0.82 (m, 8H, B-CH_2), 1.19 (s, 48H, C-CH_3), 1.41-1.51 (m, 8H, CH_2).

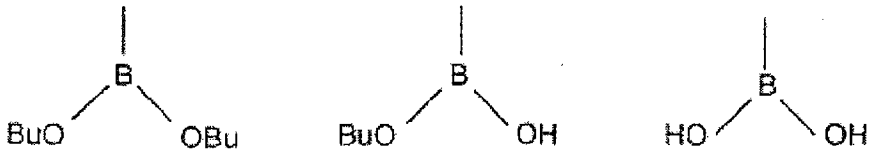
^{13}C NMR: δ = 0.66 ppm (Si-CH_3), 17.53 (Si-CH_2), 19.97 (B-CH_2), 20.24 (CH_2), 24.79 (C-CH_3), 82.73 (C).

Example 5: Hydrosilylation of allyl pinacol borane according to Example 1 with the cyclic polysiloxane of Example 4 in order to obtain 1,3,5,7-tetra-(3-(dibutoxy-boronate)propyl)-1,3,5,7-tetramethyl-cyclotetrasiloxane

Under argon, mix and heat to 70°C allyl dibutoxy borane (1.8 g, 9.1 mmoles) and Karstedt catalyst (1.10^{-4} moles of platinum per mole of allyl dibutoxy borane). After agitation, add the cyclic silane (0.5 ml, 2.1 mmoles). Then heat the solution to 70°C for 4 hours. The solvent is evaporated under reduced pressure and the volatile by-products and excess allyl dibutoxy borane extracted through kugelrohr distillation (100% C/O.2 mm Hg, or 26.6 Pa). 1.6 g of the desired product is obtained having the formula:



wherein the boronate functions are constituted essentially by a mixture of functions:



a b c

where the a functions are amply in the majority in number.

^{1}H NMR: δ = 0.03 ppm (12H, Si-CH_3), 0.48-0.57 (8H, m, Si-CH_2), 0.73-0.81 (m, 8H, B-CH_2), 0.85-0.92 (m, 24H, CH_3-CH_2), 1.24-1.56 (s, 40H, CH_2-CH_2-CH_3, Si-CH_2-CH_2)), 3.72-3.79 (m, 16H, O-CH_2)

^{13}C NMR: δ = 0.65 ppm (Si-CH_3), 13.85 (CH_2-CH_3), 17.71 (Si-CH_2), 19.06, 20.53 (CH_3-CH_2, Si-CH_2-CH_2), 33.81 (O-CH_2-CH_2), 62.92 (O-CH_2).

^{29}Si NMR: δ = -13.80, -20.79, -20.81, -20.87, -20.88, -20.94, -21.00 ppm

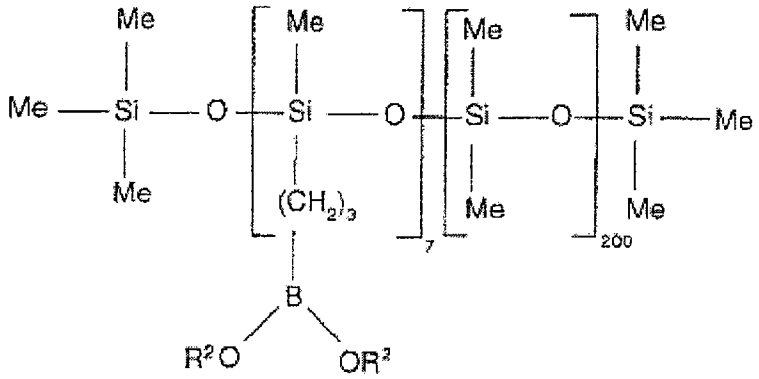
^{11}B NMR: δ = 31.16 ppm

Example 6: Synthesis of allyl diisopropyloxy borane:

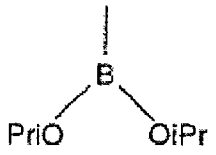
Into a 500 ml reactor under nitrogen, introduce 12 g (0.493 moles) of Mg, 170 ml of anhydrous ether and 20 g (0.141 moles) of BF_3-EtOEt. Then introduce in 1 hour a solution of 32.4 g (0.423 moles) of allyl chloride and 50 ml of dry ether. Start the preparation of magnesium by introducing an iodine crystal. The reaction is exothermic and gives rise to ether reflux. Allow the solution to react 4 hours at room temperature. Bring the reaction mass to 0°C in an ice bath. Then, in 1 hour, add 16.1 g (0.268 moles) of anhydrous isopropanol. Allow the solution to react 35 hours at room temperature. Filter over diatomaceous earth. Evaporate the filtrate and recover the reaction mass which is distilled under vacuum. 13.3 g of $H_2C=CH-CH_2B(OiPr)_2$ is recovered (isolated yield: 55%); boiling temperature: ~ 37°C /760 mmHg (1010.8 10^2 Pa). NMR and IR analyses confirm the structure of this derivate.

Example 7: Hydrosilylation of an Si-H oil by the allyl diisopropyloxy borane obtained in Example 6:

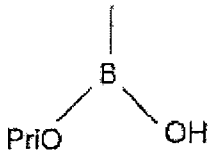
Into a 250 ml reactor under nitrogen, introduce 30 ml of dry toluene and 3.7 g (0.020 moles) of $H_2C=CH-CH_2B(OiPr)_2$. Then add 0.0314 g of the Karstedt catalyst solution (or 104 ppm of Pt metal). Bring the reaction mass to 70°C and in 1 hour pour in $MD_{200}D'_7M$ silicone oil (30 g or 0.0137 moles of SiH units). At the end of 24 hours of reaction at 80°C, the transformation rate of the SiH units is 100%. Thereafter add 2 g of carbon black and leave 1 hour at 60°C. Filter under nitrogen and by devolatilization (100°C, 1-2 mbar, or from 100 to 200 Pa), 35.4 g of a very viscous oil is recovered, the NMR and IR analyses of which confirm the following structure:



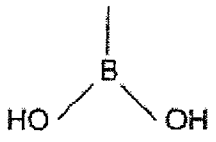
in which structure the boronate functions are constituted essentially by a mixture of functions:



a'



b'

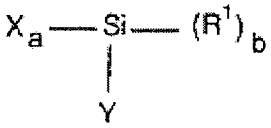


c'

where the a functions are amply in the majority in number.

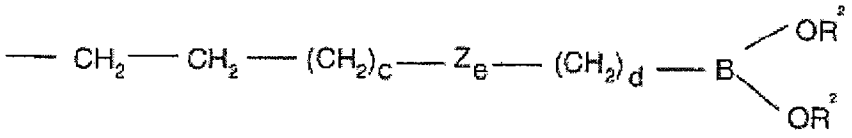
CLAIMS

1. Silane of formula (1)



wherein:

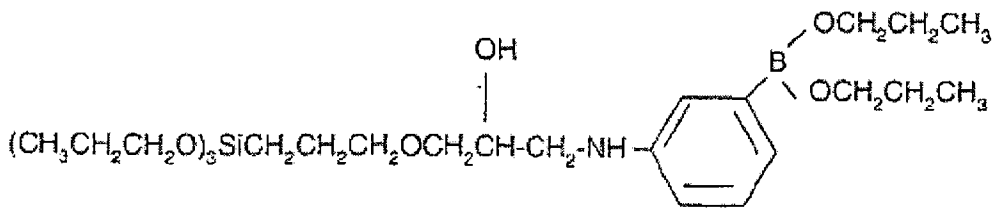
- R^1 is selected from a monovalent hydrocarbonate group, possibly substituted by halogen atoms,
- X is a hydrolyzable group,
- a is selected from among 1, 2 and 3,
- b is selected from among 0, 1 and 2,
- a + b = 3
- Y is a boronate group of formula (2)



wherein:

- c and d are integers ranging from 0 to 18
- c + d = 0 to 18
- e is selected between 0 and 1,
- Z is a divalent heterocarbon group comprising one or several heteroatoms such as O, S and/or N
- R^2 groupings, which can be identical or different, are selected from hydrogen atoms, straight or branched-chain C1-C20 aklyl radicals, preferably C1-C6, C5-C8 cycloalkyls, C6-C12 aryls, or can form with boron and oxygen atoms a heterocycle consisting of 5 to 8 elements (heterocycle atoms), preferably 5 to 6; the carbons may possibly be substituted,

being excluded the silane of formula



2. Silane according to Claim 1, characterized in that, in formula (2),
   - c + d = 0 or 1
   - e = 0
   - R^2 are straight- or branched-chain C1-C4 and/or H alkyl groupings.

3. Silane according to Claim 1, characterized in that, in formula (2),
   - c = 0 or 1
   - d = 0
   - e = 1
   - Z is a phenyl group
   - R^2 are straight- or branched-chain C1-C4 and/or H alkyl groupings.

4. Silane according to Claim 1, characterized in that, in formula (2), Z is selected from: -O-, -CO-, -COO-, phenylene, -NR'- with R' = H or straight-chain or branched C1-C4, -S-alkyl.

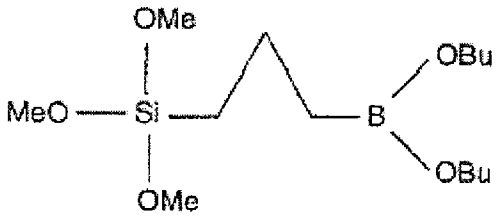
5. Silane according to any of claims 1 to 4, characterized in that, in formula (1), the radicals R^1, identical or different, are selected from:
   - C3-C10 straight-chain or branched alkyl and halogen alkyl radicals, preferably C1-C6,
   - C1-C10 cycloalkyl and halogen cycloalkyl radicals, preferably C5-C8
   - C2-C4 alkenyl radicals,
   - C6-C10 aryl and halogen aryl radicals.

6. Silane according to claim 5, characterized in that, in formula (1), the R^1 radicals, identical or different, are selected from methyl, phenyl, vinyl and trifluoro-3,3,3 propyl.

7. Silane in accordance with any of claims 1 to 6, characterized in that, in formula (1), the radical X is selected from halogen atoms, N-amino substituted, disubstituted N,N-amino, cetimonoxy, aldimonoxy, alkoxy, alkoxy alkylene-oxy, enoxy, acyloxy radicals.

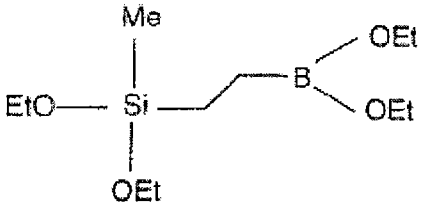
8. Silane according to claim 7, characterized in that the radical X is selected from the methoxy, ethoxy and acetoxy groupings.

9. Silane according to claim 2, having the formula:



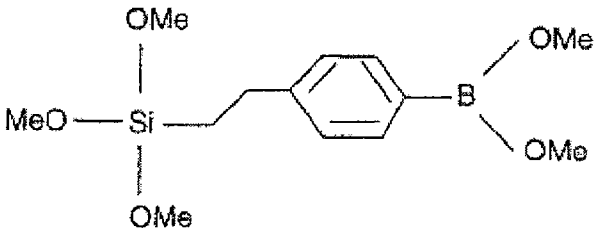
(A)

10. Silane according to claim 2, having the formula:



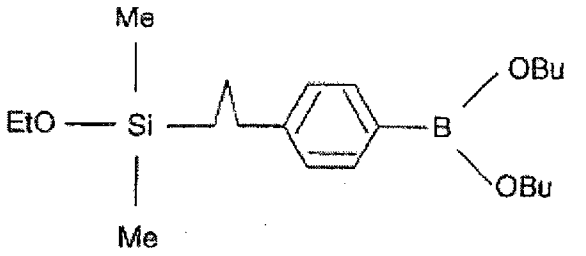
(B)

11. Silane according to claim 3, having the formula:



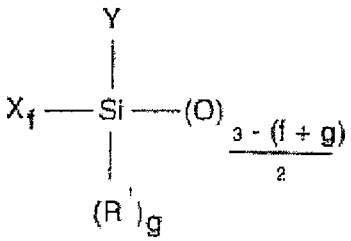
(C)

12. Silane according to claim 3, having the formula:



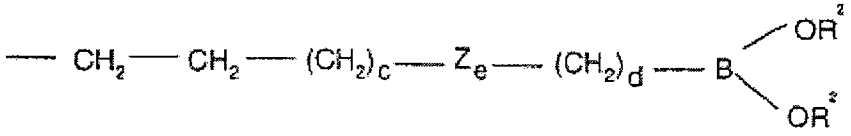
(D)

13. Polyorganosiloxane having per molecule at least one unit corresponding to the general formula (7):



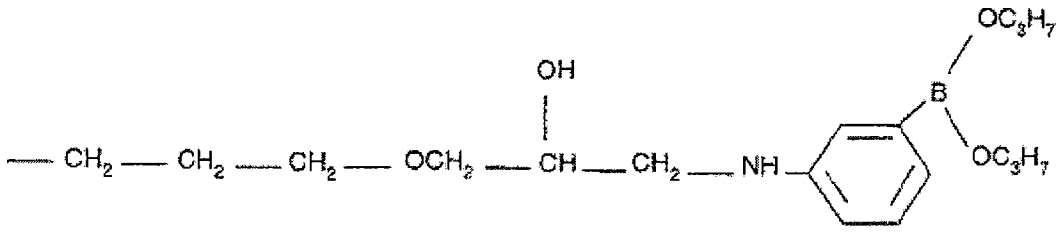
wherein:

- R^1 and X have the same meanings as claims 1 to 12,
- f is selected from among 0, 1 or 2,
- g is selected from among 0, 1 or 2,
- f + g is at most equal to 2,
- Y is a boronate group of formula (2)

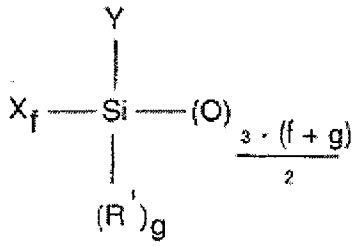


wherein:

c, Z, e, d and R^2 have the same meanings as claims 1 to 12, being excluded the polyorganosiloxane in which f + g = 0 and Y is such that:

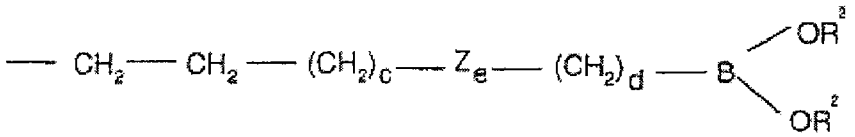


14. Polyorganosiloxane having per molecule, on the one hand, at least one unit corresponding to the general formula (7)



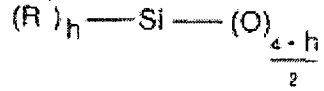
wherein:

- R^1 and X have the same meanings as claims 1 to 12,
- f is selected from among 0, 1 or 2,
- g is selected from among 0, 1 or 2,
- f + g is at most equal to 2,
- Y is a boronate group of formula (2)



wherein c, Z, e, d and R^2 have the same meanings as claims 1 without its disclaimer and 2 to 12,

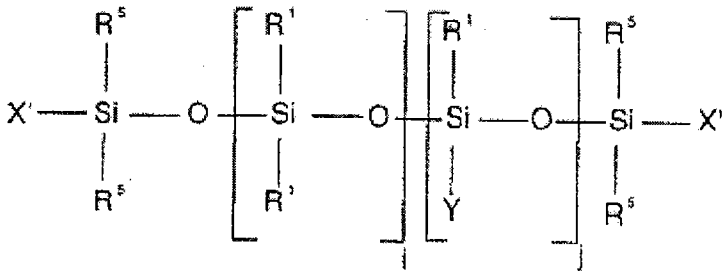
and, on the other, units corresponding to the formula (8)



wherein:

- R^1 has the same meaning as in claims 1 to 12,
- h is selected from 0, 1, 2 and 3.

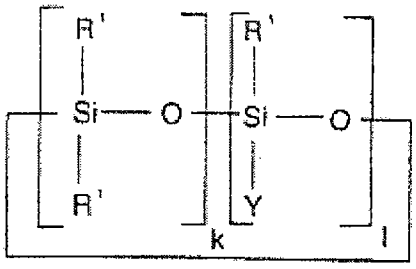
15. Polyorganosiloxane according to claim 13 without its disclaimer or 14, characterized in that it corresponds to formula (9)



wherein:

- R^1, X and Y have the same meanings as claims 13 without its disclaimer and 14,
- X' is selected from the radicals Y, R', hydroxyl and hydrogen atom,
- the radicals R^5, identical or different, are selected from the radicals R^1 and X,
- i is an integer between 0 and 1000,
- j is an integer between 0 and 50,
- if j = 0, at least 1 of the radicals X' is Y.

16. Polyorganosiloxane according to claim 13 without its disclaimer or 14, characterized in that it corresponds to formula (10)



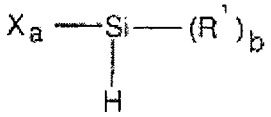
wherein:

- R^1 and Y have the same meanings as claims 13 without its disclaimer and 14,

- k is an integer between 0 and 9, inclusive,
- l is an integer between 1 and 9, inclusive,
- k + l is between 3 and 10, inclusive.

17. Process for the preparation of a silane according to claims 1 to 12, characterized in that a hydrosilylation reaction is carried out between:

- a silane of formula (3)

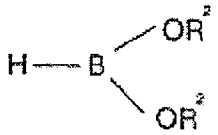


and

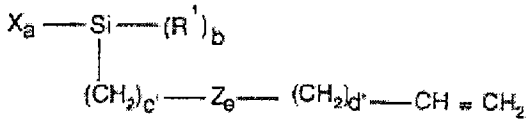
- an unsaturated alkyl dialkoxy borane of formula (4)

in which formulas (3) and (4) R^1, X, a, b, c, d, Z, e, R^2 have the same meanings as claims 1 to 12.

18. Process for the preparation of silanes according to claims 1 to 12, characterized in that a hydroboration reaction is carried out between:



(5)



(6)

wherein:

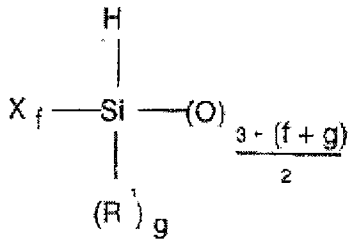
- c' = 2 to 18
- d' = 0 to 16
- c' + d' = 2 to 18

formulas (5) and (6) wherein R^2, X, a, R^1, b, Z have the same meanings as claims 1 to 12,

- with the possibility, where e = 0, that c' = 0 and d' = 1 (c' + d' = 0 or 1).

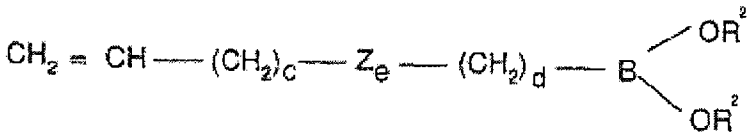
19. Process for the preparation of a polyorganosiloxane according to any one of claims 13 to 16, characterized in that a hydrosilylation reaction is carried out between:

- a polyorganosiloxane having per molecule at least unit of formula (11)



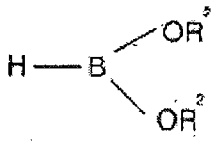
wherein R^1, g, X, f have the same meanings as claim 13 without its disclaimer or 14 and

- an unsaturated alkyl dialkoxy borane of formula (4)



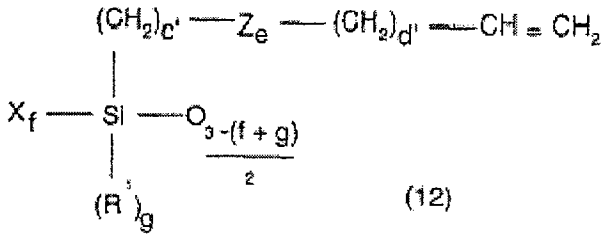
wherein R^2, c, Z, e, d have the same meanings as claims 1 without its disclaimer and 2 to 12.

20. Process for the preparation of a polyorganosiloxane according to any one of claims 6 to 9, characterized in that a hydroboration reaction is carried out by causing to react together:



(5)

and



(12)

wherein c' = 2 to 18

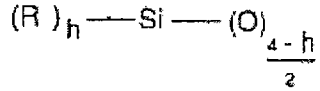
d' = 0 to 16

c' + d' = 2 to 18

in which formulas (5) and (12) R^2, X, f, R^1, g, Z and e have the same meanings as claim 13 without its disclaimer or 14,

- with the possibility, where e = 0, that c' = 0 and d' = 0 or 1 (c' +d' = 0 or 1).

21. Process for the preparation of a polyorganosiloxane according to any one of claims 13 without its disclaimer to 16, characterized in that hydrolysis and/or redistribution of a silane is carried out according to any one of claims 1 to 12 with a cyclic or straight-chain polysiloxane comprising the units of formula (8):



wherein:

- h = 2 or 3
- R^1 has the same meaning as in claims 1 to 12.

22. Process for the preparation of a polyorganosiloxane according to any one of claims 13 without its disclaimer to 17, characterized in that hydrolysis and/or redistribution of a silane is carried out according to any one of claims 1 to 12 with a hydrolysable silane of formula (13)

$$R^1_m X_n Si$$

wherein:

- m = 2 or 3
- m + n = 4
- X and R^1 have the same meanings as in claims 1 to 12.

23. Organopolysiloxane compound, storage-stable in the absence of humidity and capable of crosslinking through exposure to humidity in the absence of a crosslinking catalyst, comprising:

(A) - 100 parts by weight of at least one polydiorganosiloxane according to any one of claims 13 to 16,

(B) - from 0 to 250 parts by weight of a mineral filler.

24. Aqueous organopolysiloxane, storage-stable in the absence of humidity and capable of crosslinking through elimination of water, in the absence of a crosslinking catalyst, comprising:

(A) - 100 parts by weight of at least one polydiorganosiloxane according to any one of claims 13 to 16,

(B) - from 0 to 250 parts by weight of a mineral filler

(C) - from 0.5 to 20, preferably from 3 to 15, parts by weight of water

(D) - possibly a non-ionic, anionic, cationic or amphoteric tensioactive agent.

25. Method for conferring nonadherent and/or hydrophobic surface properties to a substrate, wherein a substrate, e.g. textile material, metal, stone or cement-based element, is coated

with a polyorganosiloxane according to any one of claims 13 to 16 or with a compound according to either of claims 23 and 24.

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ANNOUNCEMENT
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Process for the Synthesis of Substituted, Nitrogen-containing Heterocyclic Compounds

Submitters, inventors:

András Horváth	~~Károlyi Mihály út 17/b,~~ Tiszadob	80 %
Zoltán Salamon	~~Egressy Béni tér 8,~~ Debrecen	20 %

Filing date: March 31, 1995

Debrecen, January 1995

The object of our invention is a new generally usable process for preparing substituted condensed, N-substituted azoles, possibly with homo- or heterocycles, containing at least two N atoms.

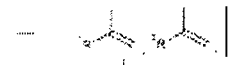
The azoles prepared according to our invention are biologically active substances that can be used as intermediates and/or as compounds with fungicidal, bactericidal, antithrombotic, inflammation-reducing, antiviral, or herbicidal effects (H. Vanden Bossche, W. Lauwers, G. Willemsens, P. Marichal, F. Cornelisson, and W. Cools. *Pestic. Sci.* **1984,** *13,* 188; G. I. Fiddler, P. Lumley, *Circulation* **1990,** *81* (Suppl. I), I 69; S. W. Wright, R. R. Harris, R. J. Collins, R. L. Corbett, A. M. Green, E. A. Wadman, and D. G. Batt, *J. Med. Chem.* **1992,** *35,* 3148; A. A. Umarov, S. S. Khalikov, M. Khaidarov, and L. A. Tyurina, *Uzh. Khim. Zh.* **1989,** *I* 40; *Chem. Abstr.* **1989,** *111,* 10920; Q. A. McKellar, and E. V. Scott, *J. Vet. Pharmacol. Ther.* **1990,** *13,* 223; S. Shirkura, A. Karasawa, and K. Kubo, *Arzneim.-Forsch.* **1991,** *42,* 1242; E. Nicolai, J. Goyard, T. Benchetrir, J. M. Teulon, F. Caussade, A. Virone, C. Delchambre, and A. Cloarec. *J. Med. Chem.* **1993,** *36,* 1175; J. A. Montgomery, S. J. Clayton, H. J. Thomas, W. M. Shannon, G. Arnett, A. J. Borner, T. K. Kion, G. L. Cantoni, and P. K. Chiang, *J. Med. Chem.* **1982,** *25,* 626; T. E. Spratt, and H. de los Santos, ***Biochemistry*** **1992,** *31,* 3688, German unexamined patent application 1,966,806, U.S. application 754,490, C.A. **1975**, *82,* 150,485).

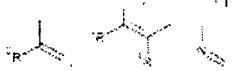
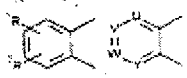
1-methyl-imidazole-5-carboxylates are key intermediates in the synthesis of physiologically active alkaloids, e.g., pylocarpin and its analogs (R. Karchlechner, M. Casutt, U. Neywang, and M. W. Schwarz, *Synthesis* **1994,** 247; J. M. Dener, L.-H. Zhang, and H. J. Rapoport, *J. Org. Chem.* **1993,** 58, 1169).

It is known (B. Testa and P. Jenner, *Drug Metab. Rev.* **1981,** *12(1),* 1-117 (p. 30); A. Wahhab, J. R. Smith, R. C. Ganter, D. M. Moore, J. Hondrelis, J. Matsoukas, and G. J. Moore, *Arzneim.-Forsch.* **1993,** *43,* 1157 (p. 1163)) that binding to cytochrome P-450 enzymes is significantly less blocked sterically in the case of azoles containing a nitrogen atom (e.g., 1,5-substituted imidazoles in contrast to 1,4-substituted imidazoles), and thus the biological effect is significantly stronger than in the case of less stable regioisomers. Cosar et al. compared the anti-trichomona or bactericidal effects of 5- and 4-nitro-1-alkyl imidazoles, and the 5-isomer turned out to be stronger in every case (C. Cosar, C. Crisan, R. Horclois, R. M. Jacob, J. Robert, S. Tchelitcheff, and R. Vaupre, *Arzeneimittel-Forsch.* **1966,** *16 (1),* 23). By proceeding according to the object of our invention, among other things, these and less stable isomers can be prepared advantageously.

The object of our invention is a process for preparing compounds of general formula 1,

where

the meaning of A is  the meaning of B is 

the meaning of D is  the meaning of BD is 

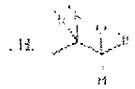
the meaning of R^1, R^2, and R^3 is H; a possibly substituted C_{1-4} alkyl; (substituted) phenyl; $NHCOC_{1-4}$ alkyl; $COOC_{1-4}$ alkyl

the meaning of U, V, W, Y, and Z is CH; N; CO; CS, N–C_{1-8}alkyl; C–OC_{1-4} alkyl; C–SC_{1-4} alkyl; C–$N(C_{1-4}$ alkyl$)_2$

the meaning of n is 0, 1

the meaning of X is a chlorine, bromine, or iodine atom; C_{1-4} alkyl–SO_2; OSO_3R^7 C_{1-3} fluoridated alkyl–SO_3, (substituted) phenyl–SO_3

the meaning of R^7 is –; possibly substituted C_{1-8} alkyl; N-containing heteroaryl

the meaning of R^8 is 

the meaning of R^4, R^5, and R^6 is H; alkyl; cycloalkyl; Q

the meaning of Q is CN; $COOC_{1-4}$ alkyl; COC_{1-4} alkyl; CO (substituted) phenyl; SO_2C_{1-4} alkyl; SO_2 (substituted) phenyl

such that

a.) the azoles characterized by general formula 2 containing an NH,

where the meaning of A, B, and D is as above, are given

with the α,β-unsaturated compounds characterized by general formula 3

where the meaning of R^4, R^5, and R^6, is as above,

with the amidine of general formula 4, which functions as a base and/or a transfer reagent,

where the meaning of E, J, and L is –; H; an aliphatic ring residue; an N-containing aliphatic ring residue,

the N-(substituted) ethylene derivative of general formula 5, forming a sub-case of formula 1.

where the meaning of A, B, D, R^4, R^5, R^6, and Q is as above,

b.) The azoles of general formula 5 are converted to a quarternary salt with the alkylizing agent of general formula 6,

where the meaning of X is as above,

then the (substituted) ethylene group is taken up selectively with a base, with the less preferred alkyl azoles of general formula 1 being removed in a Hofmann-type decomposition.

Proceeding according to point a.) of our process, the five-member N-containing heterocyclic compound of general formula 2 or its ring-condensed derivative is made to react at 0-150 °C in the presence of an organic basic catalyst of the amidine type of general formula 4, a (substituted) guanidine base, appropriately 1,5,7-triazabicyclo-[4,4,0]-dec-5-ene (TBD), its 7-methyl derivative (7-Me-TBD) , or a variant

applied to a polymer carrier (TBD-P) in a polar aprotic solvent, e.g., acetonitrile, nitromethane, acetone, dimethyl sulfoxide, N,N-dimethyl formamide, N,N-dimethyl acetamide, N-methyl-2-pyrrolidone, or a mixture thereof, advantageously acetonitrile, with 1-10 mole equivalents of an α,β-unsaturated compound of general formula 3.

- the reaction mixture – filtered in the case where a catalyst applied to a carrier is used – is evaporated,

- treated with water or an aqueous solution of an organic salt, advantageously ammonium chloride or ammonium carbonate; the product of general formula 5 forming the sub-case of formula 1, is isolated by filtering.

Proceeding according to point **b.)** of our process,

- the reaction mixture containing the product characterized by general formula 5 prepared according to point a.),

- either taking the product of general formula 5, prepared according to point a.), up in a polar solution, such as nitromethane, alcohols, dimethyl sulfoxide, N,N-dimethyl formamide, N,N-dimethyl acetamide, N-methyl 2-pyrrolidone, advantageously acetonitrile,

adding 0.001-1 mole equivalents of a halide-ion catalyst, advantageously an alkaline iodide, to the solution obtained, it is made to react with 0.9-10 mole equivalents of the alkylizing agent of general formula 6 at 0-150 °C.

- the reaction mixture is evaporated, the raw azolium salt obtained is dissolved in water, and by washing the aqueous phase with a water-immiscible solvent, an aqueous solution of the compound of general formula 7 is obtained, representing the sub-case of general formula 1.

- or the product of general formula 7 representing the sub-case of general formula 1 is obtained by adding an aprotic solvent, such as ether, acetone, or ethyl acetate, to the reaction mixture obtained and isolated by filtering,

then, to:

- the azolium salt of general formula 7,

- the reaction mixture containing it,

- or an aqueous solution

is added to the [compound] representing the sub-case of general formula 1.

0.95-5 equivalents of base, advantageously an alkali alcohol, alkali hydroxide, alkali carbonate, alkali hydrogen carbonate, or amine derivative or an alcohol and/or water solution thereof is added and stirred at 0-100 °C.

- cooled, and by treating it with water or a 10-30 % solution and/or an ammonium salt, advantageously ammonium chloride or ammonium carbonate, the separated product of general formula 1 ($n = 0$, $R^x = -$) is isolated by filtering,

- the reaction mixture obtained is stirred with some adsorbent, advantageously silica gel, aluminum oxide, purifying carbon, or a mixture thereof, and filtered, and the product of general formula I [sic]($n = 0$, $R^x = -$) is obtained by evaporating the filtrate,

- or, to the extent that it contains an organic solvent, the solvent is removed from the raw reaction mixture in vacuum, the residue is taken up into water, the water-immiscible solvent is extracted, and the organic phase is purified, dried, and evaporated.

According to the literature, azoles of general formula 2, with direct alkylization with an alkylizing agent, generally lead to mixtures in which the various regioisomers (where this is possible) and the N,N'-dialkyl quaternary azolium salts are equally present. Although they can be separated in some rare cases, in cases where regioisomers can form, the more preferred regioisomer is always formed mostly with direct alkylization.

Processes are known for separating the less preferred isomers from azoles containing a free NH group, in which the preferred N atom is protected with a protecting group during direct alkylization and the protecting group is finally split off. Thus after histidine and its derivatives are benzylized, then after the alkylization, the protecting benzyl group is hydrogenolized on a palladium catalyst (P. Sauerberg, J. Chen, E. WoldeMussie, and H. Rapoport, *J. Med. Chem.* **1989,** *32,* 1322). To synthesize trialkyl-9-methyl xanthine derivatives, 7-benzyl or 7-methoxymethyl xanthines have been used (H. G. von Schuh, German patent 1,113,696, *C.A.* **1962,** 56, 12, 909). In the case of nitroimidazoles, the acetoxymethylene protecting group can be removed by boiling in an aqueous medium (C. Bonnamas, V. Massonneau, M. Mulhauser, and N. Rouy, European patent application 325,512 (July 26, 1989); *Chem. Abstr.* **1990,** *112,* 77185). In the case of (4-substituted) imidazoles, 1,2,4-triazole, and benzotriazole, an acyl group can likewise be removed by hydrolysis (R. A. Olofson and R. V. Kendall, *J. Org. Chem.* **1970,** *35,* 2246; C. Kashima, Y. Harada, and A. Hosomi, *Heterocycles* **1993,** *35,* 433; T. Kamijo, R. Yamamoto, H. Harada, and K. Iizuka, *Chem. Pharm. Bull.,* **1983,** *31(4), 1213).* In the case of urocanic acid (imidazole-4-acrylic acid), phenacyl can be removed with the acetic-acid/zinc system (N. Lauth-de Viguerie, N. Sergueeva, M. Damiot, H. Mawlawi, M. Riviere, and A. Lattes, *Heterocycles* **1994,** *37,* 1561).

The alkyl-type protective groups (benzyl, phenacyl, acyloxymethylene) have the common disadvantage that they are not taken up regioselectively: the protected azole can be obtained only with a low yield and purity. Using an acyl (acetyl, ethoxycarbonyl, benzyl) protective group is more advantageous from this viewpoint; they are said to be taken up regioselectively. However, the protected azoles obtained in this way, because of their characteristic of strong electron absorption, can only be removed by using alkylizing agents that are very active and difficult to prepare (trialkyl oxonium tetrafluoroborates) or can be quaternized [only] at a high temperature and pressure (up to 7000 bars). It is also known that the acylized azoles compounds are difficult to store and decompose due to the effect of moisture.

According to previous literature or our own experience, because of regioselectivity, in the case of azoles of general formula 2, the cyanoethyl group is a special alkylizing agent.

Imidazoles have been made to react thermically with (substituted) acrylonitrile (N. Sawa and S. Okamura, *Nippon Kagaku Zasshi* **1969**, *90(7)*, 704; *Chem. Abstr.* **1969,** *71,* 10173. M. Yamauchi and M. Masui, *Chem. Pharm. Bull.* **1976,** *24(7),* 1480. W. B. Wright, J. B. Press, US patent *4,619,941* (October 28, 1986); *Chem. Abstr.* **1987,** *106,* 102285).

4-aryl imidazole has been cyanoethylized with a basic catalyst in ethanol in the presence of potassium hydroxide (M. A. Iradyan, A. G. Torsyan, R. G. Mirzoyan, I. P. Badalyants, Z. S. Isaakyan, D. Sh. Manucharyan, M. Kh. Dayan, G. S. Sakanyan, I. A. Dzagatspanyan, N. E. Akonayn,

Y. Xh. Ter-Zaharyan, and A. A. Aroyan, *Khim-Pharm. Zh.* **1977,** *11,* 42; *Chem. Abstr.* **1978,** *88,* 22759y, or with quaternary ammonium-hydroxide catalysts, in various solvents – primarily dioxane, such as 4-nitroimidazole with benzyl-triethyl/trimethyl ammonium hydroxide (C. Cosar, C. Crisan, R. Horclois, R. M. Jacob, J. Robert, S. Tchelitcheff, and R. Vaupre, *Arzneimittel-Forsch.* **1966,** *16(1),* 23), benzoimidazole (J. Diamond, and R. A. Wohl, *European patent application 34,116* (August 19, 1981); *Chem. Abstr.* **1981,** *95,* 203961), 5-nitro and 2-methyl-5-nitrobenzoimidazole (A. M. Efros, *Zhur. Obsh. Khim.* **1960,** *30,*3565; *Chem. Abstr.* **1961,** *55,* 18712d).

Imidazole has been made to react with phenylvinyl ketone with a hydroxide catalyst (S. V. Bogatkov, B. M. Kormanskaya, V. Mochalin, and E. M. Cherkasova, *Khim. Geterotsikl. Soedin.* **1971,** *7(5),* 662-4; *Chem. Abstr.* **1972,** *76,* 59525).

Under various conditions, Michael additions of 1,2,3-triazole or benzotriazole have been investigated with a catalyst of benzyl-trimethyl ammonium hydroxide or pyridine (R. H. Wiley, N. R. Smith, D. M. Johnson, and J. Moffat, *J. Am. Chem. Soc.* **1954,** 76, 4933). The reaction of 2-methyl 4-nitroimidazole with 5 kinds of Michael acceptors with numerous catalysts in various solvents [has been studied], and the pyridine /dimethyl-sulfoxide system has been found to be the best. Under such conditions, acrylonitrile was made to react at 135 °C for 10 hours (A. K. S. B. Rao, C. G. Rao, and B. B. Singh, *J. Org. Chem.***1990,** *55,* 3702). Catalysis with other tertiary amines has been described in the reaction of imidazole and methyl acrylate in the presence of triethylamine [has been studied] (S. V. Bogatkov, B. M. Kormanskaya, V. Mochalin, and E. M. Cherkasova, *Khim. Geterotsikl. Soedin.* **1971,** *7(5), 662-4; Chem. Abstr.* **1972,** *76,* 59525). Derivatives of xanthine of natural origin [have been studied], such as theophillin with acrylonitrile in the presence of copper with a catalyst of sodium hydroxide or benzyl-trimethyl ammonium hydroxide (K. Doebel and H. Spiegelberg. US patent 2,761,862 (1956); *Chem. Abstr.* **1957,** *51,* 3676; A. Rybar and L. Stibrányi, *Collect. Czech Chem. Commun.* **1973,** *38(5),* 1571). Theophillin and theobromine have been made to react with the reagents acrylonitrile, acrylic acid, and ethyl acrylate in the presence of benzyl-trimethyl ammonium hydroxide (R. Zelnik and M. Pesson, *Bull. Chem. Soc. Fr.* **1959,** 1667).

These processes generally require high temperatures and long reaction times, which lead to a destruction of regioselectivity and to side reactions (e.g., polymerization of the Michael acceptor, addition of components of the non-azole type in the system). The side reactions and the use of solvents with high boiling points make it difficult to obtain the product from the reaction mixture, reduce the yield, and ruin the quality of the product.

A cyanoethyl protecting group has also been used in the alkylization of imidazole and benzoimidazole (A. Horváth, *Synthesis,* **1994,** 104), but the process given is complex, and requires a processing step associated with large loss of materials (acidic re-solution and extraction, realkalinization, reextraction). Regioselectivity was not investigated at that time. Some of the bases used (sodium hydroxide, sodium alcoholate) cannot be used in the case of azoles substituted with strongly electron-absorbing groups (for example, nitroimidazoles), where from the quaternary salt of N-alkyl-N'-cyanoethyl azolium, splitting of the alkyl group, not the cyanoethyl group is preferred, or in the case of molecules sensitive to nucleophilic bases (for example, the phthalimide ring opens due to the effect of these bases).

The advantage of the process according to our invention is that, on the one hand, azoles of formula 2 containing an NH group and ring-condensed derivatives can be made to react as a base and/or transfer reagent that causes a strong, non-nucleophilic Michael addition in the presence of an amidine or guanidine of general formula 4, which makes a more stable compound of general formula 3, the Michael acceptor forming the sub-case of general formula 1, possible by a fast reaction under mild conditions, at a low temperature (mostly at room temperature), with a high yield, practically without side reactions, with regioselectivity favored kinetically. It can be used as well as an intermediary in the conversion of the Q-electron-absorbing functional group – to give N-(substituted) ethylene derivatives that are Michael adducts that can be prepared with high yield and purity by simple methods. The practically fully selective conversion makes it possible in many cases that, in the case of further alkylization, the Michael adducts cannot be isolated from the reaction mixture.

On the other hand, the process according to our invention makes it possible to use the Michael adducts as N-protected azoles in a position preferred for the production of less preferred N-substituted regioisomers: by alkylizing the N,N'-substituted azolium salts of general formula 7 obtained with alkylizing agents – isolating them, if necessary, compounds are usually obtained that can be isolated as crystals and can be expected to have other advantageous characteristics – *in situ,* under conditions of a Hofmann-type decomposition, by splitting the (substituted) ethyl group selectively; the product obtained is a (less preferred) N-substituted derivative of the starting azole. Both the quaternization and decomposition of the quaternary salt can be performed practically quantitatively, under mild conditions, and the final products are obtained regioselectively, with high yield and high purity.

Using a cyanoethyl or substituted derivative as a protective group is especially advantageous in the cases of alkylization when the products of general formula 1 are slightly soluble in water and the quaternary salts are obtained by filtering from the decyanoethylization reaction mixture. Using a 2-(alkoxycarbonyl) ethyl protective group is advantageous in the case of final products of general formula 1 that are soluble in water, because when the protective group is split off, a β-substituted propionic-acid salt is formed that dissolves well in water, but poorly in organic solvents, and does not contaminate the products extracted into the organic solvent.

To synthesize the less preferred N-substituted regioisomers of azoles, C-substituted with strongly groups with a electron-absorbing effect, containing a free NH group, it is advantageous to use ethyl protective groups substituted in the 2-position with a keto or sulfonyl group, which make it possible for them to be removed with weak, non-nucleophilic bases, thus decomposition of quaternary azolium salts containing a strongly election-absorbing group or groups sensitive to nucleophiles (ring opening, aromatic nucleophilic substitution) can be performed without side reactions.

Details of our process will be presented in the following examples, without limiting our invention to them.

Examples

1.) 4-phenyl-1H-imidazole-1-propionic-acid nitrile

4.32 g 4-phenyl imidazole, 3.6 ml acrylonitrile, and 0.14 g TBD are stirred in 10 ml acetonitrile for 10 minutes, a solution of ammonium chloride is added to the residue obtained by evaporation, it is cooled and stirred, filtered, washed, and dried. Yield. 5.65 g (95 %), m.p.: 114-115.5 °C.

2.) 4-nitro-1H-imidazole-1-propionic-acid nitrile

5.65 g 4-nitroimidazole, 5 ml acrylonitrile, and 0.28 g TBD are stirred in 15 ml DMSO at 100 °C for 5 hours. It is processed by evaporation similar to example 1. Yield: 7.8 g (94 %). By recrystallizing from ethyl acetate, m.p.: 112-113 °C.

3.) α,4-dimethyl-1H-benzoimidazole-1-propionic-acid nitrile

2.64 g 4-methyl benzoimidazole, 1.67 g crotonic-acid nitrile, and 0.14 g TBD are stirred in 10 ml acetonitrile at 50 °C for 1 hour. It is evaporated and processed in the manner of the previous example. Yield: 3.82 g (96 %), m.p.: 117-118 °C. ^{1}H NMR ($CDCl_3$): 1.89 (d, 3H, J= 7.1), 2.69 (s, 3H), 2.88-2.98 (m, 2H), 4.83 (sext, 1H, J= 7.1), 7.10-7.17 (m, 1H), 7.18-7.31 (m, 2H), 8.03 (s, 1H). MS(EI^+, 70 eV): m/z (%): 199 (M^+, 28). 159 (100), 131 (15), 77 (161).

4.) 1H-1,2,4-triazole-1-propionic-acid nitrile

34.52 [g] 1,2,4-triazole, 50 ml acrylonitrile, and 0.7 g TBD are taken up into 50 ml acetonitrile, stirred for 4 hours, and evaporated. Yield: 65.16 g, m.p.: 36-37 °C (hexane-EtOAc). [^{1}H] NMR ($CDCl_3$): 3.00 (t, 2H). 4.47 (t, 2H). 8.01 (s, 1H). 8.23 (s, 1H).

5.) 1H-1,2,4-triazole-1-propionic-acid ethyl ester

6.9 g 1,2,4-triazole, 12 g acrylic-acid ethyl ester, and 0.28 g TBD are taken up into 20 ml acetonitrile, stirred for 5 hours, then evaporated. The raw product is purified by eluting with a 100:5 chloroform:methanol mixture. 15.8 g (93 %) of oil is obtained. ^{1}H NMR ($CDCl_3$): 1.23 (t, 3H), 2.91 (t, 2H), 4.14 (q, 2H), 4.48 (t, 2H), 7.93 (s, 1H), 8.16 (s, 1H).

6.) 3-(4-methyl-1H-imidazole-1-yl)-pentane-dicarbonic-acid diethyl ester

8.2 g 4-methyl imidazole, 18.6 g diethyl gutaconate, and 0.7 g TBD in 20 ml acetonitrile are allowed to stand for 40 days, then evaporated. The raw product is clarified from a dilute solution of hydrochloric acid. Its germicidal effect is set to pH 8 with ammonia solution, then it is extracted with dichloromethane. The organic phase is dried and evaporated. Yield: 18.2 g (68 %).

7.) 1-(phenylmethyl)-5-methyl 1H-imidazole

2.68 g of the product obtained according to example 6 and 1.88 g benzyl bromide in 5 ml acetonitrile were boiled under reflux cooling for 3 hours and evaporated. 10 ml of a 2-M ethanol solution of NaOEt is added, evaporated after 10 minutes of stirring, acidified with cold dilute hydrochloric acid, and washed with ether. The aqueous phase was clarified at room temperature, set to pH 8 with ammonia solution, cooled, dried, and

washed with water. Yield: 1.04, m.p.: 107-109.5 °C (hexane ether). ^{1}H NMR ($CDCl_3$): 2.08 (s, 3H), 5.04 (s, 2H), 6.82 (m, 1H), 6.98-7.10 (m, 2H), 7.22-7.40 (m, 3H), 7.46 (m, 1H).

8.) 1-(2-cyanoethyl)-4-phenyl-3-methyl-1H-imidazolium bromide

4.61 g 4-phenyl imidazole, 2.6 ml acrylonitrile, and 1 g TBD-P are stirred at room temperature in 20 ml acetonitrile for 130 hours and filtered. 4.3 ml methyl iodide is added to the filtrate. It is boiled for 6 hours under reflux cooling, cooled, filtered, washed with acetone, and dried. Yield: 9.0 g (83 %), m.p.: 179.5-180.5 °C (acetonitrile). ^{1}H NMR (DMSO-d_6): 3.27 (t, 2H), 3.88 (s, 3H), 4.56 (t, 2H), 7.60 (s, 5H), 8.06 (m, 1H), 9.34 (m, 1H).

9.) 1-(2-cyanoethyl)-3-(cyanopropyl)-4-phenyl-1H-imidazolium bromide

1.97 g of the product prepared according to example 1.), 1.48 g 4-bromobutyronitrile, and 0.015 g NaI are boiled in nitromethane under reflux cooling, cooled, diluted with 20 ml ether, filtered, washed with ether, and dried. Yield: 3.21 g (93 %), m.p.: 131-132 °C (MeCN). ^{1}H NMR (DMSO-d_6): 1.99 (quint, 2H, J= 7.2), 2.58 (t, 2H, J= 6.7), 3.33 (t, 2H, J= 6.2), 4.33 (t, 2H, J= 7.2), 4.60 (t, 2H, J= 6.2), 7.60 (s, 5H), 8.11 (d, 1H, J= 1.5), 9.60 (d, 1H, J=1.5).

10.) 1-(2-cyano-1-methylethyl)-3-(3-cyanopropyl)-4-methyl-1H-benzoimidazolium bromide

Proceeding according to example 9 from 1.99 g of the product of example 3.) and 1.48 g 4-bromobutyronitrile. Yield: 32.6 g (94 %), m.p.: 187-188 °C (nitromethane). ^{1}H NMR (DMSO=d_6): 1.78 (d, 3H, J= 6.6), 2.30 (quint, 2H, J= 6.5), 2.77 (t, 2H, J= 6.5), 2.81 (s, 3H), 3.40 (d, 2H, J= 6.0), 4.74 (t, 2H, J= 6.5), 5.44 (sext, 1H, J= 6.0), 7.49 (d, 1H, J= 7.0), 7.61 (t, 1H, J= 7.0), 8.07 (d, 1H, J= 7.0), 10.13 (s, 1H).

11.) 1-(2-cyanoethyl)-4-(3-cyanopropyl)-1H-1,2,4-triazolium bromide

Proceeding according to example 9 from 1.22 g 1H-1,2,4-triazole-1-propionic-acid nitrile. Yield: 20.5 g (76 %), m.p.: 104-105.5 °C. ^{1}H NMR (DMSO-d_6): 2.20 (quint, 2H), 2.66 (t. 2H), 3.21 (t, 2H), 4.39 (t. 2H), 4.63 (t, 2H), 9.35 (s, 1H), 10.28 (s, 1H).

12.) 1-(2-cyanoethyl)-3-(phenylmethyl)-4-phenyl-1H-imidazolium bromide

1.97 g of the product of example 1 and 1.71 g benzyl bromide in 5 ml acetonitrile are boiled for 50 hours under reflux cooling, diluted with ether, and filtered. Yield: 3.49 g (95 %), m.p.: 173-174 °C (acetonitrile). ^{1}H NMR (DMSO-d_6): 3.30 (t, 2H, J= 6.1), 4.60 (t, 2H, J= 6.1), 5.55 (s, 2H), 7.05-7.14 (m, 2H), 7.31 (m, 3H), 7.50 (m, 5H), 8.10 (d, 1H, J= 1.3), 9.47 (d, 1H, J= 1.3).

13.) 1-(2-cyano-1-methylethyl)-3-(phenylmethyl)-4-methyl-1H-benzoimidazolium bromide

Proceeding according to point 12.) from 1.99 g of the product of point 3.) and 1.71 g benzyl bromide (reaction time: 20 hours). [Yield:] 3.55 g, m.p.: 214-215 °C (acetonitrile). ^{1}H NMR (DMSO-d_6): 1.85 (d, 3H, J= 6.7), 2.49 (s, 3H), 3.50 (d, 2H, J= 6.2), 5.51 (sext, 1H, J= 6.2), 6.01 (s, 2H), 7.18-7.30 (m, 2H), 7.35-7.50 (m, 4H), 7.62 (t, 1H, J= 7.8), 8.13 (d, 1H, J= 7.8), 10.30 (s, 1H).

14.) 1-(2-cyanoethyl)-4-(phenylmethyl) 1H-1,2,4-triazolium bromide

Proceeding according to point 12.) from 1.22 g 1H-1,2,4-triazole-1-propionic-acid nitrile and 1.71 g benzyl bromide. Yield: 2.38 g (81 %), m.p. 166.5-168 °C. ^{1}H NMR (DMSO-d_6): 3.23 (t, 2H), 4.71 (t, 2H), 5.57 (s, 2H), 7.40-7.54 (m, 5H), 9.43 (s, 1H), 10.28 (s, 1H).

15.) 1-(2-(ethyoxycarbonyl)ethyl-4-(phenylmethyl) 1H-1,2,4-triazolium bromide

Proceeding according to point 12.) from 4.23 g of the product of point 5.) and 4.28 g benzyl bromide. Yield: 7.28 g (85 %), m.p.: 116-117 °C. ^{1}H NMR (DMSO-d_6): 1.17 (t, 3H), 3.05 (t, 2H), 4.10 (q. 2H), 4.67 (t, 2H), 5.63 (s, 2H), 7.42-7.61 (m, 5H), 9.46 (s, 1H), 10.42 (s, 1H).

16.) 1-(2-cyano-1-methylethyl)-3-(2-propenyl)-4 methyl-1H-benzoimidazolium bromide

Proceeding according to point 12 from 1.99 g of the product of point 3.) and 1.3 g allyl bromide. Yield: 2.88 g (90 %), m.p.: 180-182 °C (acetonitrile). ^{1}H NMR (DMSO-d_6): 1.78 (d, 3H, J= 7.1), 2.74 (s, 3H), 3.42 (d, 2H, J= 7.1), 5.01 (m, 1H), 5.30-5.54 (m, 2H + 1H), 6.16-6.40 (m, 1H), 7.47 (d, 1H, J= 7.5), 7.61 (t, 1H, J= 7.5), 8.07 (d, 1H, J= 7.5), 10.06 (s, 1H).

17.) 1-(2-cyanoethyl)-3-(((((4-methylcarbonyl)phenyl)amino)carbonyl)methyl)-4-phenyl-1H-imidazolium bromide

1.97 g of the product of point 1.) and 2.72 g 2-bromo-N-((4-methoxycarbonyl)phenyl)acetamide in 10 ml acetonitrile are boiled under reflux heating, cooled, diluted with acetonitrile, filtered, washed, and dried. Yield: 4.41 g (94 %), m.p.: 205-207 °C (MeOH). ^{1}H NMR (DMSO-d_6): 3.32 (t, 2H, J= 6.9), 3.82 (s, 3H), 4.68 (t, 3H, J=6.9), 5.28 (s, 2H), 7.55-7.60 (m, 5H), 7.63 (m, 2H), 7.94 (m, 2H), 8.11 (d, 1H, J= 1.2), 9.58 (d, 1H, J= 1.2), 10.84 (s, NH).

18.) 1-(2-cyano-1-methylethyl)-3-(((((4-methoxycarbonyl)phenyl)amino)carbonyl)methyl)-4-methyl-1H-benzoimidazolium bromide

Proceeding according to point 17.) from 1.99 g of the product of point 3.) and 2.72 g 2-bromo-N-((4-methoxycarbonyl)phenyl) acetamide. [Yield:] 4.48 g (95 %), m.p.: 141-143 °C (MeOH). ^{1}H NMR (DMSO-d_6): 1.39 (d, 3H, J= 7.2), 2.67 (s, 3H), 3.43 (d, 2H, J= 7.2), 3.82 (s, 3H) 5.49 (sext, 1H, J= 7.2), 5.72 (s, 2H), 7.48 (d, 1H J= 7.1), 7.64 (t, 1H, J= 7.1), 7.76 (m, 2H), 7.98 (m, 2H), 8.10 (d, 1H, J= 7.1), 10.05 (s, 1H), 11.17 (s, NH).

19.) 1-(2-cyanoethyl)-4-(((((4-methoxycarbonyl)phenyl)amino)carbonyl)methyl)-1H-1,2,4-triazolium bromide

Proceeding according to point 17.) from 1.22 g 1H-1,2,4-triazole 1-propanoic-acid nitrile and 2.72 g 2-bromo-N-((4.-methoxycarbonyl)phenyl) acetamide (1 hour). [Yield:] 3.66 g (93 %), m.p.: 227-228 °C (Me OH). ^{1}H NMR (DMSO-d_6): 3.28 (t, 2H), 3.84 (s, 3H), 4.83 (t, 2H), 5.42 (s, 2H), 7.74 (d, 2H), 7.98 (d, 2H), 9.30 (s, 1H), 10.22 (s, 1H), 11.01 (s, NH).

20.) 4-(2-cyanoethyl)-1-(((((4-methoxycarbonyl)phenyl)amino)carbonyl)methyl)-1H-1,2,4-triazolium bromide

Proceeding according to point 17 from 0.30 g 4H-1,2,4-triazole-4-propionic-acid nitrile and 0.67 g 2-bromo-N-((4-methoxycarbonyl)phenyl)acetamide. Yield: 0.41 g (42 %), m.p.: 206-208 °C (MeOH).

^{1}H NMR (DMSO-d_6): 3.32 (t, 2H), 3.84 (s, 3H), 4.73 (t, 2H), 5.59 (s, 2H), 7.74 (d, 2H), 7.97 (d, 2H), 9.41 (s, 1H), 10.34 (s, 1H), 11.10 (s, NH)

21.) 5-phenyl-N-((4-methoxycarbonyl)phenyl)-1H-imidazole 1-acetamide

2.35 g of the product of point 17.) in 5 ml of a 2-M methanol solution of NaOMe, is stirred for 5 minutes at room temperature, cooled, and treated with an aqueous solution of ammonium chloride, stirred for 2 hours, filtered, washed with water then cold acetone, and dried. Yield: 1.61 g (96 %), m.p.: 220-222 °C (methanol/water). ^{1}H NMR (DMSO-d_6): 3.89 (s, 3H), 4.82 (s, 2H), 7.18 (d, 1H, J= 1.1), 7.30-7.45 (m, 5H), 7.51 (m, 2H), 7.67 (d, 1H, J= 1.1), 7.99 (m, 2H + NH).

22.) 7-methyl-N-((4-methoxycarbonyl)phenyl 1H-benzoimidazole-1-acetamide

Treating 2.36 g of the product of point 18.) according to point 21.). Yield: 1.57 g (97 %), m.p.: 242-244 °C (MeOH/water). ^{1}H NMR (DMSO-d_6): 2.65 (s, 3H), 3.88 (s, 3H), 5.15 (s, 2H), 7.08 (d, 1H, J= 7.4), 7.19 (t, 1H, J= 7.4), 7.49-7.68 (m, 2H + 1H), 7.96 (m, 2H), 8.61 (s, NH).

23.) N-((4-methoxycarbonyl)phenyl) 4H-1,2,4-triazole 4-acetamide

Treating 1.97 g of the product of point 19.) according to point 21.) Yield: 1.19 g (91 %), m.p.: 280-282 °C (MeOH). ^{1}H NMR (DMSO-d_6): 3.82 (s, 3H), 5.07 (s, 2H), 7.72 (d, 2H), 7.95 (d, 2H), 8.49 (s, 2H), 10.74 (s, NH).

24. N-((4-methoxycarbonyl)phenyl)-1H-1,2,4-triazole 1-acetamide

Based on point 21.) from 0.4 g of the product of point 20.). Yield: 0.22 g (85 %), m.p.: 218-220 °C (MeOH). ^{1}H NMR (DMSO-d_6): 3.83 (s, 3H), 5.19 (s, 2H), 7.72 (d, 2H), 7.95 (d, 2H), 8.01 (s, 1H), 8.56 (s, 1H), 10.76 (s, NH).

25. 5-phenyl-1-methyl 1H-imidazole

8 g of the product of point 8.) in 8 ml of a 20% sodium-hydroxide solution is stirred at room temperature for 1 hour, cooled, filtered, washed, and dried. Yield: 3.61 g (97 %), m.p.: 90.5-93 °C.

26. 5-phenyl-1-(phenylmethyl) 1H-imidazole

1.84 g of the product of point 12.) is treated according to point 25.). Yield: 1.05 g (90 %), m.p.: 115-117 °C. ^{1}H NMR ($CDCl_3$): 5.15 (s, 2H), 6.96-7.07 (m, 2H), 7.14 (d, 1H, J= 0.9), 7.24-7.42 (m, 8H), 7.57 (d, 1H, J= 0.9).

27.) 1-(phenylmethyl)-7-methyl 1H-benzoimidazole

1.85 g of the product of point 13.) is treated according to point 25.). Yield: 0.98 g (88 %), m.p.: 159-160 °C. ^{1}H NMR ($CDCl_3$): 2.47 (s, 3H), 5.67 (s, 2H), 6.92-7.05 (m, 3H), 7.18 (t, 1H, J= 8.2), 7.25-7.39 (m, 3H), 7.70 (d, 1H, J- 8.2), 7.87 (s, 1H).

28.) 5-phenyl-1H-imidazole-1-butanoic-acid nitrile

Proceeding according to point 9.), the reaction mixture obtained is evaporated, and the quaternary salt is stirred with 10 ml of a 20% sodium-lye solution at room temperature for 1 hour and extracted with ethyl acetate, and the organic phase

is extracted with 20 ml of 1-N solution of HCl. The aqueous phase is clarified, and the pH is set to between 8 and 9 with an ammonia solution and extracted 3 times with 20 ml dichloromethane, and the organic phase is dried and evaporated. Yield: 1.96 g (93 %), m.p.: 58-59 °C. ^{1}H NMR ($CDCl_3$): 1.88 (quint, 2H, J= 7.0), 2.17 (t, 2H, J= 7.0), 4.19 (t, 2H, J= 6.9), 7.10 (d, 1H, J= 1.0), 7.30-7.52 (m, 5H), 7.60 (d, 1H, J= 1.0).

29.) 7-methyl-1H-benzoimidazole-1-butanoic-acid nitrile

By making the reaction mixture containing the quaternary salt obtained according to point 10.) react according to point 28.) and processing, the yield is 1.89 g (95 % with respect to the product according to 3.)). ^{1}H NMR ($CDCl_3$): 2.17 (quint, 2H, J= 6.7), 2.35 (t, 2H, J= 6.7), 2.68 (s, 3H), 4.49 (t, 2H, J= 6.7), 7.03 (d, 1H, J= 8.4), 7.17 (t, 1H, J= 8.4), 7.65 (d, 1H, J= 8.4), 7.85 (s, 1H). Picrate, m.p.: 199-201 °C (EtOH).

30.) 7-methyl-1-(2-propenyl) 1H-benzoimidazole

2.56 g of the reaction mixture containing the quaternary salt obtained according to point 16.) is reacted according to point 28.) and processed. Yield: 1.24 g (90 %). ^{1}H NMR ($CDCl_3$): 2.63 (s, 3H), 4.78-4.99 (m, 3H), 5.17-5.28 (*m, 1H), 5.96-6.17 (m, 1H), 7.00 (d, 1H, J= 7.3), 7.15 (t, 1H, J= 7.3), 7.65 (d, 1H, J= 7.3), 7.81 (s, 1H).

31.) 4-(2-propenyl)-4H-1,2,4-triazole oxalate

1.22 g 1H-1,2,4-triazole-1-propanoic-acid nitrile and 1.3 g allyl bromide in 5 ml acetonitrile are boiled under reflux cooling for 10 hours. The raw product obtained is dissolved in 10 ml acetone. It is treated in a solution prepared with 1.26 g (0.01 mol) oxalic-acid dihydrate and 3 ml EtOH, cooled, filtered, washed with acetone, dried. Yield: 1.39 g (73 %), m.p.: 97-99 %. Base: boiling point$_3$: 167-170 °C.

32.) 4-(phenylmethyl)-4H-1,2,4 triazole

3.40 g of the product of point 15.) and 1 g NaOH in a solution prepared with 30 ml methanol are boiled under reflux cooling for 0.5 hour. After recooling, the reaction mixture is stirred with 8 g silica gel for 0.5 hour at room temperature, dried, and evaporated. The raw product is taken up in 30 ml chloroform, stirred with 5 g silica gel and 2 g clarifying carbon for 0.5 hour and filtered, and the filtrate is evaporated. Yield: 1.46 g (92 %). Recrystallizing from an ether-hexane mixture: [m.p.:] 113-114 °C.

33.) 4H-1,2,4-triazole-4-butanoic-acid nitrile

1.69 g of the product of point 5.) and 1.48 g 4-bromobutyronitrile in 5 ml nitromethane are boiled for 22 hours under reflux cooling. It is evaporated, the quaternary salt is treated according to point 32.), the raw product is dissolved in 10 ml acetone, treated with a solution of 1.26 g (0.01 mol) oxalic-acid dihydrate in 3ml ethanol solution, and washed with acetone. Yield: 1.45 g (64 %), m.p.: 93-95 °C (acetone). Base: ^{1}H NMR ($CDCl_3$): 2.20 (quint, 2H), 2.43 (t, 2H), 4.26 (t, 2H), 8.23 (s, 2H).

34.) 1-methyl 1H-imidazole

68.08 g imidazole, 105 g ethyl acrylate, and 1.39 g TBD are stirred for 1 hour in 100 ml acetonitrile. 130 g dimethyl sulfate is dripped in over 0.5 hour. It is boiled for 1 hour under reflux cooling. The reaction mixture is evaporated. It is dissolved in 200 ml water and treated with a mixture of 100 g sodium hydroxide and

100 ml water. It is stirred for one hour at room temperature, then extracted 5 times with 100 ml ethyl acetate. The organic phase is dried and evaporated, and the residue is distilled. Yield: 72.2 g (88 %), b.p. 195-197 °C.

35.) 1-(phenylmethyl) 1H-benzoimidazole

11.8 g benzoimidazole, 11 g ethyl acrylate, and 0.14 g TBD are boiled in 30 ml acetonitrile under reflux cooling for 1 hour, then 13 g benzyl chloride is added to it, and it is boiled for 20 more hours. The solvent is distilled off, the evaporation residue is taken up in 50 ml water and treated with 10 g NaOH and 15 ml water. It is stirred for 1 hour at room temperature, then for 2 hours at 0-4 °C. The precipitate product is filtered, washed with water, and dried. Yield: 14.9 g (71 %), m.p.: 116-118 °C.

36.) 1-ethyl-5-phenyl 1H-imidazole

5 g 4-phenyl imidazole, 3.7 g ethyl acrylate, and 0.14 g TBD in 20 ml acetonitrile are stirred for 1 hour, then 5.6 g diethyl sulfate are added, and it is evaporated under reflux cooling for 20 hours, then evaporated. The evaporation residue is taken up in 50 ml water and treated with 3.2 g sodium-hydroxide at room temperature. After 1 hour of stirring, the reaction mixture is extracted twice with 30 ml ethyl acetate. The combined organic phase is dried and evaporated. Yield: 5.4 g (89 %) of product, b.p. 109-110 °C (0.4 mmHg).

37.) 5-phenyl-1-(2-propenyl) 1H-imidazole

In a manner similar to example 36.), starting from 2.88 g 4-phenyl imidazole, 2.2 g ethyl acrylate, 0.07 g TBD, and 3.6 g allyl bromide, 3.17 g (86 %) of product is obtained. ^{1}H NMR ($CDCl_3$): 4.52-4.61 (m, 2H), 4.97-5.30 (m, 2H), 5.83-60.5 (m, 1H), 7.11 (d, 1H, J= 1.1), 7.34-7.46 (m, 5H), 7.57 (d, 1H, J= 1.1). Picrate, m.p.: 127-128 °C (ethanol).

38.) 4-(2-propenyl)-4H-1,2,4-triazole oxalate

3.45 g 1,2,4-triazole, 4 ml acryl nitrile, and 0.14 g TBD in 10 ml acetonitrile are stirred for 3 hours, then 10 g allyl bromide is added to it over 4 hours under reflux cooling. It is boiled and evaporated. The evaporation residue is treated as described in example 36.). The raw product is dissolved in 50 ml acetone and treated with a boiling solution prepared from 6.3 g oxalic-acid dihydrate and 15 ml ethanol. It is cooled and stirred for 4 hours, filtered, and washed with acetonitrile. Yield: 6.33 g (64 %) of an isomer-pure crystalline product, m.p.: 97-99 °C.

39.) 4-butyl-4H-1,2,4-triazole oxalate

6.76 g raw 1H-1,2,4-triazole-1-propanoic-acid ethyl ester, 20 ml butyl bromide, and 0.30 g sodium iodide in 20 ml nitromethane are boiled for 20 hours under reflux cooling, then evaporated. The quaternary salt is converted according to point 38.). Yield: 4.98 g (58 %), m.p.: 109-11 °C. Base: ^{1}H NMR ($CDCl_3$): 0.95 (t, 3H), 1.36 (sext, 2H), 1.80 (quint, 2H), 4.02 (t, 2H), 8.16 (s, 2H).

40.) 4-(2-butyl) 4H-1,2,4-triazole

1.22 g raw 1H-1,2,4-triazole-1-propanoic-acid nitrile, 5.4 ml 2-bromobutane, and 0.15 g sodium iodide in 5 ml nitromethane are boiled for 60 hours under reflux cooling, then evaporated. The residue is purified according to point 36.) by column chromatography, eluting with a 9:1 (by volume) mixture of acetone and methanol. Yield: 0.58 g (47 %). ^{1}H NMR ($CDCl_3$): 0.83 (t, 3H), 1.48 (d, 3H), 1.77 (quint, 2H), 4.15 (sext, 1H), 8.13 (s, 2H).

41.) 1-(phenylmethyl)-1H-imidazole-5-carbonic-acid ethyl ester

1.26 g imidazole-4-carbonic-acid methyl ester, 1 g crotonic-acid nitrile, and 0.03 g TBD are boiled under reflux cooling for 1 hour, then 1.71 g benzyl bromide is added, and it is stirred for 60 more hours, the evaporated. The evaporation yield is taken up in 10 ml of a 2-M ethanol solution of Na ethylate, stirred for 10 minutes at room temperature, then for 20 minutes at 60 °C. Treated with 20 ml of a 10% ammonium-chloride solution. Stirred for 20 hours at room temperature, filtered, washed with cold water, and dried. Yield: 1.82 g (79%), m.p.: 64-65 °C.

42.) 1-methyl-1H-imidazole-5-carbonic-acid ethyl ester

1.26 g imidazole-4-carbonic-acid methyl ester, 1 g crotonic-acid nitrile, and 0.03 TBD are boiled for 1 hour under reflux cooling, then 1.05 ml (1.38 g) dimethyl sulfate is added, and it is boiled for 3 more hours and evaporated. The residue is taken up in 10 ml of a 2-M ethanol solution of ammonium chloride, stirred for 60 minutes at room temperature, cooled, treated with 20 ml of a 10% ammonium-chloride solution, stirred for 20 hours, filtered, and washed. Yield: 1.05 g (75 %), m.p.: 54-56 °C.

43.) 4-nitro-1-(3-oxobutyl) 1H-imidazole

2.26 g 4-nitroimidazole, 2 ml (1.71 g) methylvinyl ketone, and 0.14 g TBD are boiled in 25 ml acetonitrile under reflux cooling for 1 hour, then evaporated. The evaporation residue is treated with 10 ml of a 10% solution of ammonium chloride, cooled, filtered, and washed with water. Yield: 3.41 g (93 %), m.p.: 73-74.5 °C (EtOAc). ^{1}H NMR ($CDCl_3$): 2.10 (s, 3H), 3.11 (t, 2H), 4.22 (t, 2H), 7.83 (d, 1H), 8.36 (d, 1H).

44.) 7H-theophillin-7-propanoic-acid nitrile

3.6 g theophillin and 0.14 g TBD in 15 ml acrylonitrile for 120 hours and evaporated, and the raw product is treated according to point 43.). Yield: 4.3 g (95 %), m.p.: 159-161 °C. Recrystallizing from EtOAc: m.p.: 160-161 °C.

45.) 3-phenyl-1H-1,2,4-triazole-1-propanoic-acid nitrile

[Proceeding] according to point 44.) from 2.90 g 3-phenyl-1H-1,2,4-triazole. Yield: 3.65 g (92 %), m.p.: 86.5-88 °C. ^{1}H NMR ($CDCl_3$): 3.04 (t, 2H), 4.45 (t, 3H), 7.37-7.52 (m, 3H), 8.02-8.15 (m, 2H), 8.20 (s, 1H).

46.) 3-phenyl-1H-pyrazole-1-propanoic-acid nitrile

[Proceeding] according to point 44.) from 2.88 g 3-phenyl pyrazole. Yield: 3.43 g (87 %), m.p.: 51-53 °C (ether-hexane). ^{1}H NMR ($CDCl^3$): 3.00 (t, 2H), 4.42 (t, 2H), 6.58 (d, 1H), 7.30-7.48 (m, 3H), 7.52 (d, 1H), 7.78 m, 2H).

47.) 1H-benzotriazole-1-propanoic-acid nitrile and 2H-benzotriazole-2-propanoic-acid nitrile

Proceeding according to point 44.) from 2.38 g benzotriazole and purifying the raw product by chromatography (eluent: 95:5 chloroform:acetone). Yield: 2.26 g (66 %), m.p.: 78-80 °C.

48.) 1-methyl-5-nitro-1H-imidazole

a) 2.26 g 4-nitroimidazole, 1.6 ml acrylonitrile, and 0.07 g TBD in 10 ml acetonitrile are boiled for 8 hours under reflux cooling. 2.1 ml (2.78 g) dimethyl sulfate is added, and it is boiled for 3 more hours. The mixture is cooled, 3.16 ml (3.37 g) 7-methyl-1,5,7-triazabicyclo-[4,4,0]-dec-5-ene (7-Me-TBD) is stirred in over 0.5 hour at room temperature. It is evaporated on a column filled with silica gel and eluted with a mixture of ethyl acetate and acetone (2:1). Yield: 1.45 g (57 %), m.p.: 52-54 °C.

b) 1.45 g 4-nitro-1-(3-oxobutyl) 1H-imidazole and 0.76 ml (1.01 g) dimethyl sulfate in 5 ml acetonitrile are boiled for 4 hours under reflux cooling. It is cooled, and 2.76 g ground potassium carbonated is assed with mixing. It is stirred for 10 hours at room temperature, filtered, evaporated, and chromatographed according to what is described at point a). Yield: 0.87 g (87 %), m.p.: 53-55 °C.

49.) 7-(3-oxobutyl) 7H-theophillin

5.4 g theophillin, 2.7 ml (2.31 g) methylvinyl ketone, and 0.14 g TBD in 20 ml acetonitrile are boiled for 3 hours under reflux cooling. It is evaporated, and the residue is taken up in 40 ml of a 10% HCl solution and dried at 60-70 °C. The filtrate is cooled, the germicidal effect is set to pH 8 with a 25% ammonium solution. It is crystallized at 0-4 °C, filtered, and washed. Yield: 6.31 g (84 %), m.p.: 138.5-140 °C (ethyl acetate).

50.) 5-methyl-5H-imidazo-(4,5-c)-pyridine oxalate

1.19 g 5-azabenzoimidazole, 1 ml (0.8 g) acrylonitrile, and 0.014 g TBD in 5 ml acetonitrile are stirred at room temperature for 0.5 hour, then 0.75 ml (1.7 g) methyl iodide is added, and it is stirred for 4 more hours. It is evaporated, 5 ml of a 20% sodium-hydroxide solution is added, and it is stirred for 4 more hours. A saturated salt solution is added, and it is extracted with 5-30 ml dichloromethane. The organic phase is dried, clarified, and evaporated, and the residue is dissolved in 10 ml acetone. It is treated with a solution prepared from 1.26 g oxalic acid in 5 ml boiling ethanol, cooled, filtered, and washed with acetone. Yield: 0.98 g (44 %), m.p.: 188-190 °C (EtOH).

51.) 5-(phenylmethyl)-5H-imidazo-(4,5-c) oxalate

Using 1.71 g benzyl bromide as the alkylizing agent according to point 50.) and a quaternarization time of 20 hours. Yield: 1.08 g (33 %), m.p.: 142-143.5 °C (EtOH).

52.) β-methyl-1H-imidazole-1-propanoic-acid nitrile

13.6 g imidazole, 18.5 ml (15 g) methacrylonitrile, and 0.3 g TBD in 30 ml acetonitrile are boiled under reflux cooling for 100 hours. 5-5 ml methacrylonitrile is added every 24 hours

to the mixture. It is evaporated. Yield: 27.96 g. ^{1}H NMR ($CDCl_3$): 1.29 (d, 3H), 3.08 (sext, 1H), 4.13 (d, 2H), 7.05 (s, 1H), 7.56 (s, 1H).

53.) 1-(2-phthalimidoethyl) 1H-imidazole

1.36 g imidazole, 1.7 ml (1.32 g) acrylonitrile, and 0.03 g TBD in acetonitrile are boiled under reflux cooling for 0.5 hour. 5.1 g 2-bromoethyl phthalimide is added, and it is boiled for 8 more hours and cooled. 35 ml ether is added. It is crystallized at 0-5 °C and filtered. The raw quaternary salt is dissolved in 200 ml methanol. 2.88 ml (3.06 g) 7-Me-TBD is added to it, and it is stirred for 5 hours, evaporated, treated with 20 ml of a 100-g/l solution of ammonium chloride, stirred at 0-5 °C, filtered, washed, and dried. Yield: 4.39 g (91 %), m.p.: 165-167 °C (2-propanol).

54.) 5-phenyl-1-methyl 1H-pyrazole

1.97 g 3-phenyl-1H-pyrazole-1-propanoic-acid nitrile and 1.05 ml (1.38 g) dimethyl sulfate in 5 ml acetonitrile are boiled for 15 hours under reflux cooling. 1.58 ml (1.69 g) 7-Me-TBD are added at 10-15 °C, it is stirred for 5 hours and evaporated, and the residue is treated with 10 ml of a 100 g/l solution of ammonium chloride. It is extracted 3 times with 20 ml chloroform. The combined organic phase is dried, clarified, and evaporated, and the residue (1.37 g) is purified by distillation. Yield: 0.94 g (59 %), $b.p._{12}$ 118 °C.

55.) 3-phenyl-4-methyl 4H-1,2,4-triazole

1.98 g 3-phenyl-1H-1,2,4-triazole-1-propanoic-acid nitrile is treated according to example 54.), and the raw product is crystallized from petroleum ether / ethyl acetate.
Yield: 1.00 g (63 %), m.p.: 111-113 °C.

56.) 1,3,9-trimethyl xanthine (isocaffeine)

1.4 g 7H-theophillin-7-propanoic-acid nitrile and 0.7 ml (0.88 g) dimethyl sulfate in 5 ml acetonitrile are boiled for 15 hours under reflux cooling. 1 ml (1.07 g) 7-Me-TBD is added at 10-15 °C, it is stirred at room temperature and evaporated, and 5 ml ethanol is added, it is stirred at 0-5 °C, filtered, washed with a mixture of cold ethanol and water. Yield: 0.91 g (78 %), m.p.: 294-295 °C (EtOH-water).

57.) 4-acetamino-1-(2-cyanoethyl)-3-(phenylmethyl)-imidazolium bromide

1.78 g (0.01 mol) 4-acetamino-1H-imidazole-1-propanoic-acid nitrile and 2.56 g (0.015 mol) benzyl bromide in 20 ml Me CN are boiled for 16 hours under reflux cooling, then cooled, and the precipitated crystalline product is filtered, washed with acetone, and dried. Yield: 3.05 g (87 %), m.p.: 194-196 °C.

58.) 3-(N-acetyl-N-(1-phenylmethyl-1H-imidazole-5-yl))amino-propanoic-acid nitrile and 5-acetamino-1-(phenylmethyl) 1H-imidazole

2.4 g (6.9 mmol) 4-acetamino-1-(2-cyanoethyl)-3-(phenylmethyl)-imidazolium bromide and 2.1 ml (2.13 g, 14 mmol) diazabicyclo-undecene (DBU) in 10 ml MeCN are stirred at 50 °C for 0.5 hour. It is evaporated, the evaporation residue is treated with

15 ml of a 10% ammonium-chloride solution, and it is extracted 3 times with 20 ml dichloromethane. The organic phase is evaporated, the residue is eluted in a silica-gel column with 9:1 acetone:methanol. The first fraction obtained is 3-(N-acetyl-N-(1-(phenylmethyl)-1H-imidazole-5-yl))amino-propanoic-acid nitrile): 0.72 g, m.p.: 112-114 °C (EtOAc). ^{1}H NMR (DMSO-d_6): 1.36 (s, 3H), 2.56-2.72 (m, 2H), 2.73-2.91 (m, 1H), 4.02-4.22 (m, 1H), 5.08 (m, 2H), 6.94 (s, 1H), 7.19-7.43 (m, 5H), 7.92 (s, 1H). MS (EI$^+$, 70 eV) (m/z, %): 268 (M^+, 3), 226 (8), 186 (27), 91 (100). IR (KBr): 1574, 1671, 2255 cm^{-1}. The second fraction is 5-acetamino-1-(phenylmethyl)-1H-imidazole: 0.40 g, m.p.: 149-151 °C (10:1 toluene:n-butanol). ^{1}H NMR (DMSO-d_6): 1.98 (s, 3H), 5.05 (s, 2H), 6.75 (s, 1H), 7.08-7.20 (m, 2H), 7.26-7.41 (m, 3H), 7.49 (s, 1H), 9.59 (NH). MS (EI$^+$, 70 eV) (m/z, %): 215 (M^+, 9), 173 (18), 91 (100).

59.) 5-acetamino-1-(phenylmethyl) 1H-imidazole

2.96 g (8.5 mmol) 4-acetamino-1-(2-cyanoethyl)-3-(phenylmethyl)-imidazolium bromide is added to 50 ml of a 2-M methanol solution of MeONa (0.1 mol MeONa) with stirring. After 5 minutes, 4.9 g ammonium chloride is added to the mixture, then 10 g silica gel is added, and it is mixed for 0.5 hour. It is filtered, the filtrate is evaporated, and the residue is crystallized from a toluene:n-butanol mixture. Yield: 1.20 g (66 %), m.p.: 150-152 °C.

60.) E-1-(2-cyanoethyl)-1H-imidazole-4-propenic-acid ethyl ester

3.32 g (0.02 mol) E-1H-imidazole-4-propenic-acid ethyl ester (urocanic-acid ethyl ester), 1.45 ml (1.17 g, 0.022 mol) acrylonitrile, and 0.14 g (1 mmol) TBD in MeCN are stirred at room temperature for 10 hours, then crystallized at -18 °C for 24 hours and filtered. Yield: 4.03 g (92 %), m.p.: 120-121.5 °C (EtOH). ^{1}H NMR ($CDCl_3$): 1.31 (t, 3H), 2.84 (t, 2H), 4.16-4.33 (m, 4H), 6.57 (d, 1H, J= 15 Hz), 7.22 (m, 1H), 7.55 (d, 1H, J= 15 Hz), 7.59 (m, 1H). MS (EI$^+$, 70 eV) (m/z, %): 219 (M^+, 27), 174 (100), 147 (46), 104 (25).

61.) 4-nitro-1H-benzoimidazole-1-propanoic-acid nitrile

3.1 g (19 mmol) 4-nitro-benzoimidazole, 20 ml acrylonitrile, 2.45 g (20 mmol) 4-(dimethylamino)-pyridine, and 0.14 g (1 mmol) TBD in 10 ml MeCN are stirred at 70 °C for 6 hours, then cooled, crystallized at -18 °C, and filtered. Yield: 3.8 g (88 %), m.p.: 195-196 °C (acetone). ^{1}H NMR (DMSO-d_6): 3.19 (t, 2H), 4.72 (t, 2H), 7.52 (t, 1H), 8.10 (dd, 1H), 8.25 (dd, 1H), 8.63 (s, 1H). MS (EI$^+$. 70 eV) (m/z, %): 216 (M^+, 100), 186 (68), 146 (33), 118 (94).

62.) α-4-dimethyl-1H-imidazole-1-propanoic-acid-nitrile oxalate

1.64 g (0.02 mol) 4-methyl imidazole and 1.45 ml (1.17 g, 0.022 mol) acrylonitrile) in 8 ml MeCN are quaternized at a temperature of 80 °C for 5 hours, then evaporated, and the evaporation residue is dissolved in 5 ml acetone and treated with a solution of 2.52 g (0.02 mol) oxalic-acid dihydrate and 5 ml EtOH. It is cooled, and the precipitated crystals are filtered and washed with acetone. Yield: 3.11 g (65 %), m.p.: 104-105.5 °C (EtOH). ^{1}H NMR (DMSO-d_6): 1.51 (d, 3H, J- 6.8 Hz), 2.20 (d, 3H, J= 0.9 Hz), 3.17 (d, 2H, J= 6.6 Hz), 4.77 (sext, 1H, J= 6.7 Hz), 7.38 (m, 1H), 8.51 (d, 1H, J=1.5 Hz). MS (EI$^+$, 70 eV) (m/z, %): 149 (base M^+, 48), 109 (100), 81 (43).

63.) E-1-(2-propenyl)-1H-imidazole-5-propenic-acid ethyl ester

3.29 g (0.015 mol) E-1-(2-cyanoethyl)-1H-imidazole-4-propenic-acid ethyl ester, 1.7 ml (2.43 g, 0.02 mol) allyl bromide, and 0.5 g NaI in 20 ml MeCN are quaternized at a temperature of 50 °C for 120 hours. After cooling, 3 ml (3.04 g, 0.02 mol) diazabicyclo-

undecene (DBU) is added at a temperature of 10 °C, then stirred at a temperature of 25 °C for 0.5 hour and evaporated. The evaporation residue is treated with 30 ml of a 10% ammonium-chloride solution, then extracted 3 times with 20 ml dichloromethane. The organic phase is evaporated, and the evaporation residue is eluted with acetone in a short silica-gel column. Yield: 2.75 g (89 %), m.p.: 120 °C.

64.) 1-(pivaloyloxy)methyl-5-methyl 1H-imidazole

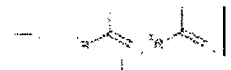
2.39 g (0.01 mol) α-4-dimethyl-1H-imidazole-1-propanoic-acid-nitrile oxalate is added to 35 ml of a 10% ammonia solution at a temperature of 10 °C, with stirring, then the mixture obtained is extracted 3 times with 20 ml dichloromethane. The organic phase is evaporated, 5 ml MeCN, 1.6 ml (1.66 g, 0.011 mol) pivalinic-acid chloromethyl ester, and 0.2 g NaI are added to the evaporation residue, it is stirred at a temperature of 25 °C for 10 days, then diluted with 15 ml EtOC, cooled, and filtered. The 2.4 g of imidazolium salt obtained are dissolved in 20 ml MeCN, and it is treated at a temperature of 10 °C with 1.65 ml (1.67 g, 0.011 mol) diazabicyclo-undecene (DBU), then stirred at a temperature of 25 °C for 0.5 hour. It is evaporated, and the residue is treated with 30 ml of a 10% ammonium-chloride solution, then extracted 3 times with 20 ml dichloromethane. The organic phase is evaporated, and the residue is chromatographed in a silica-gel column with a mixture of EtOAc and MeOH. Yield: 1.02 g (52 %), colorless oil. ^{1}H NMR ($CDCl_3$): 1.18 (s, 9H), 2.27 (d, 3H, J= 1.0 Hz), 5.80 (s, 2H), 6.78 (m, 1H), 7.61 (m, 1H). MS (EI^+, 70 eV) (m/z, %): 196 (M^+, 7), 95 (20), 94 (28), 57 (100).

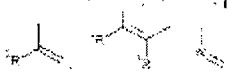
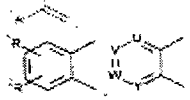
65.) 5-bromo-1-methyl 1H-imidazole

2.94 g (0.02 mol) 4-bromoimidazole, 1.79 ml (1.48 g, 0.022 mol) crotonic-acid nitrile, and 0.14 g (1 mmol) TBD in 15 ml acetonitrile are stirred at 80 °C for 3 hours, 2.1 ml (2.77 g, 0.022 mol) dimethyl sulfate is added, then it is stirred at this temperature for 3 more hours. It is cooled to 10 °C, 3.3 ml (3.34 g, 0.022 mol) DBU, is stirred for half an hour at 25 °C, and the mixture is evaporated. The residue is treated with 30 ml of a 10% aqueous solution of ammonium-chloride solution and extracted 3 times with 20 ml dichloromethane. The organic phase is evaporated, and the residue is eluted on silica gel with acetone. Yield: 2.74 g (85%). Melting point: 44-46 °C.

Claims

1. A process for preparing N-alkylized azoles containing at least two nitrogen atoms (general formula 1), where

the meaning of A is  the meaning of B is 

the meaning of D is  the meaning of BD is 

the meaning of R^1, R^2, and R^3 is H; a C_{1-4} alkyl, possibly substituted;

(substituted phenyl); $NHCOC_{1-4}$ alkyl; $COOC_{1-4}$ alkyl

the meaning of U, V, W, Y, and Z is CH; N; CO; CS, N–C_{1-8}alkyl; C–OC_{1-4} alkyl; C-OC_{1-4} alkyl; C–$N(C_{1-4}$ alkyl$)_2$

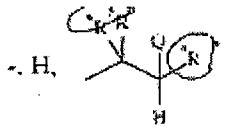
the meaning of n is 0, 1

the meaning of X is a chlorine, bromine, or iodine atom; C_{1-4} alkyl–SO_3; OSO_3R^7 C_{1-4} fluoridated alkyl–SO_3, (substituted) phenyl–SO_3

the meaning of R^7 is –; possibly substituted C_{1-8} alkyl; N-containing heteroaryl

the meaning of R^8 is

illegible



the meaning of R^4, R^5, and R^6 is H; alkyl; cycloalkyl; Q

the meaning of Q is CN; $COOC_{1-4}$ alkyl; COC_{1-4} alkyl; CO (substituted) phenyl; SO_2C_{1-4} alkyl; SO_2 (substituted) phenyl

azoles containing at least two unsubstituted nitrogen atoms (general formula 2, where the meaning of A, B, and D is as above) and olefins with an electron-absorbing group (general formula 3, meaning of R^4, R^5, and R^6 as above, in a reaction, characterized in that a.) the reaction is run is the presence of substituted amidine (general formula 4, where the meaning of E, J, and L is –, H, an aliphatic ring reside, an N-containing aliphatic ring residue) functioning as a base and or a transfer reagent.

b.) the N-monoalkyl azole obtained (general formula 5, where the meaning of A, B, D, R^4, R^5, and R^6 is as above), some alkylizing agent (general formula 6, where the meaning of X and R^7 is as above), possibly in the presence of an alkali-halide catalyst, the quaternary azolium salt (general formula 7, where the meaning of A, B, D, Q, X, R^4, R^5, R^6, and R^7 is as above, and the (substituted) ethyl substituent containing the electron-absorbing group Q is split off selectively with an appropriately selected base.

2. A process according to claim 1/a above, characterized in that 1,5,7-triazabicyclo-[4,4,0]-dec-5-ene or 7-methyl-1,5,7-triazabicyclo-[4,4,0]-dec-5-ene is used appropriately as a basic catalyst, by itself or applied to a polymer carrier.

3. A process according to claims 1/a and 2 above, characterized in that the ethylene derivative is appropriately used in a molar excess, possibly as a solvent.

4. A process according to claims 1/a, 2, and 3 above, characterized in that the product is isolated by evaporating the mixture, treating it with water, a solution of an inorganic aqueous salt, appropriately ammonium chloride or ammonium carbonate, and filtering.

5. A process according to claim 1/b, characterized in that the Michael adduct (general formula 5) is made to react with 0.9-10, appropriately 1-5 equivalents of alkylizing agent, possibly without isolation, *in situ*.

6. A process according to either of claims 1/b and 5, characterized in that the azolium salt formed (general formula 7) is isolated by evaporating the reaction mixture or diluting it with an aprotic solvent and filtration.

7. A process according to any of claims 1/b, 5, and 6, characterized in that the azolium salt is treated without isolation or by isolation in an alcohol and/or aqueous solution at 0-100 °C, with 0.95-5 equivalents of a base.

8. The process according to claims 1/b and 5-7, characterized in that the product is isolated by evaporation, treating it with water, an aqueous solution of an inorganic salt, appropriately ammonium chloride or ammonium carbonate, and filtering.

9. A process according to claims 1/b and 5-8, characterized in that the product is isolated by evaporating the mixture, stirring the residue with water, and extracting it with a water-immiscible organic solvent.

10. A process according to claims 1-9, characterized in that the Michael addition and/or alkylization is performed using a polar aprotic solvent, appropriately acetonitrile or nitromethane at 0-150 °C, appropriately 20-120 °C.

[2 signatures]

+ 1 page of drawings
[signature]

Diagrams

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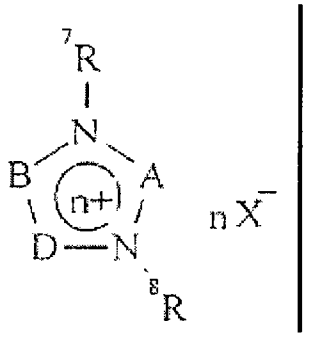

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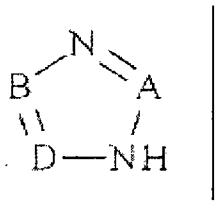

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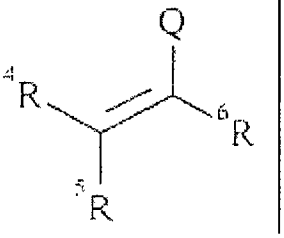

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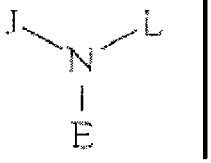

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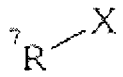

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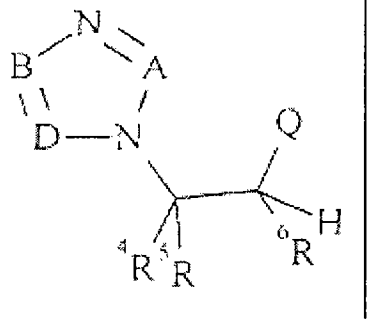

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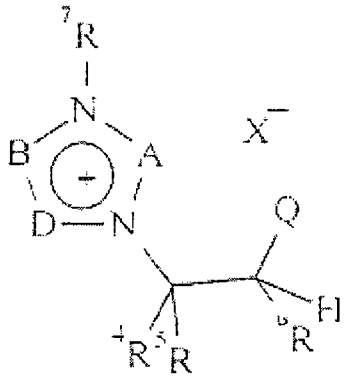

7.

[2 signatures]

Lapsed

HPO e-register (in Hungarian)

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Application date: 1995.03.31

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Publication number: 78019

Publication date: 1999.05.28

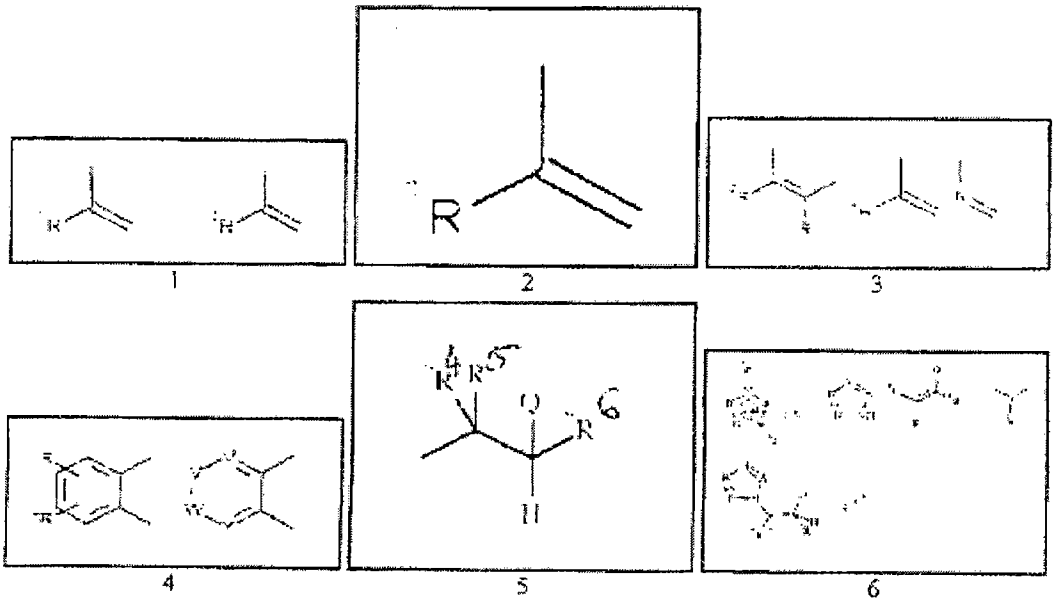
IPC: C07D-233/10; C07D-233/14; C07D-233/16; C07D-233/18

Hungarian title: **Eljárás szubsztituált nitrogéntartalmú, heterociklusos vegyületek szintézisére**

English title: PROCESS FOR THE PREPARATION OF SUBSTITUTED, NITROGEN CONTAINING HETEROCYCLIC COMPOUNDS

Applicant and inventor: Horváth András, Tiszadob (HU), 80%
Salamon Zoltán, Debrecen (HU), 20%

Representative: Salamon Zoltán, Debrecen (HU)



Abstract (first publication):

The object of the invention is a process for producing azoles of general formula (1) in the diagram

The meaning of A is

The meaning of B is

The meaning of D is

The meaning of BD is

The meaning of R^1, R^2, and R^3 is H, possibly a substituted C_{1-4} alkyl, (substitute) phenyl, $NHCOC_{1-4}$alkyl, or $COOC_{1-4}$alkyl; the meaning of U, V, W, Y, and Z is CH, N, CO, CS, NC_{1-8}alkyl, COC_{1-4}alkyl, CSC_{1-4}alkyl, or $CN(C_{1-4}alkyl)_2$; the meaning of n is 0 or 1; the meaning of X is a chlorine, bromine, or iodine atom, C_{1-4}alkyl SO_3, OSO_3R^7, C_{1-4} fluoridated alkyl SO_3, or (substituted) phenyl SO_3; the meaning of R^7 is –, H, possibly a substituted C_{1-8} alkyl or N-containing heteroaryl; the meaning of R^8 is – or H; the meaning of R^4, R^5, or R^6 is H, alkyl, cycloalkyl, or Q; the meaning of Q is CN, $COOC_{1-4}$alkyl, COC_{1-4}alkyl, CO (substituted) phenyl, SO_2C_{1-4}alkyl or SO_2 (substituted) phenyl.

According to the procedure, the unsubstituted azole (general formula 2) containing at least two N atoms

is made to react in the presence of a catalyst of the organic-amidine type (general formula 4, where the meaning of E, J, and L, is H, an aliphatic ring residue, or an N-containing aliphatic ring residue) in a polar, aprotic solvent or solvents, with substituted ethylene derivatives with an electron-absorbing group Q (general formula 3), while proceeding according to the process, the product (general formula 1 ($n = 0$, $R^8 = -$), is obtained by proceeding according to process B), making the N-monosubstituted azole (general formula 5) in a polar solvent by adding a catalyst with a halogen atom, and an alkylizing agent (general formula 6), the a base).

Measures

0. Data publication (A0)
Measure Date: 1995.04.04 *Announcement:* 1995.05.29 (AA1A Communication of patent application data)

5. Publication of patent application (CV)
Measure Date: 1999.03.30 *Announcement:* 1999.05.28 (BB9A Publication of patent applications)

8. Lapse of provisional patent protection due to non-payment of fees (EF)
Measure Date: 2000.01.13 *Reception:* 2000.01.19 *Announcement:* 2000.02.28 (FD9A Lapse of provisional patent protection due to non-payment of fees)

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UNION OF SOVIET SOCIALIST REPUBLICS
USSR STATE COMMITTEE FOR INVENTIONS AND DISCOVERIES

(19) **SU** (11) **851,940 A1**

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DESCRIPTION OF AN INVENTION
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(22) March 20, 1980

(46) April 30, 1988, Bulletin No. 16

(71) Institute of Physicoorganic Chemistry and Coal Chemistry of the Ukrainian SSR Academy of Sciences, and the Zaporozh'ye Medical Institute

(72) O. G. Eilazyan, K. M. Khabarov, Yu. M. Yutilov, and P. N. Steblyuk

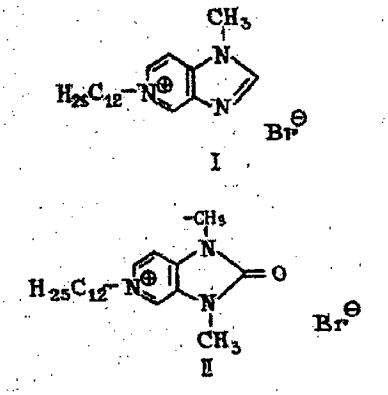
(53) 547.836.3 (088.8)

(56) U.S. Patent No. 3,919,193, classification 260-211.5, 1975.

M. D. Mashkovskii, *Medicinal Drugs*, Meditsina Publishers, Moscow, 1972, Vol. 2, p. 340.

(54) QUATERNARY SALTS OF IMIDAZO[4,5-*c*]PYRIDINIUM EXHIBITING ANTIMICROBIAL AND FUNGISTATIC ACTIVITY

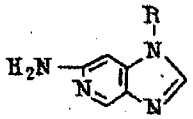
(57) Quaternary salts of imidazo[4,5-*c*]pyridinium having formula I or II:



which exhibit antimicrobial and fungistatic activity.

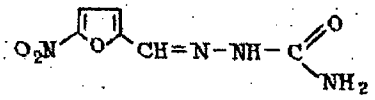
The invention relates to new biologically active chemical compounds, specifically to quaternary salts of imidazo[4,5-*c*]-pyridinium, which exhibit antimicrobial and fungistatic activity.

Derivatives of 4-oxy-7-amino-imidazo[4,5-*c*]pyridine having the following formula are known:



where R is β-ribofuranosyl or the 2′,3′,5′–O–C_1 to C_8 acylated analogue, which exhibit antiviral activity.

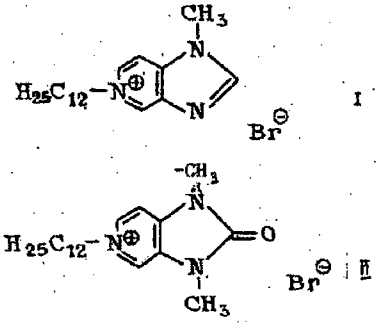
Also known is the drug furacilin:



which is used as an antimicrobial agent.

The object of the invention is to expand the toolkit of agents for acting on the living organism.

The stated object is attained by the novel chemical compounds — quaternary salts of imidazo[4,5-*c*]pyridinium having formula I or II:



which are obtained by reacting dodecylbromide with the corresponding imidazo[4,5-*c*]pyridine while it is being heated in a solvent medium.

The end product obtained — quaternary salts of imidazo[4,5-*c*]pyridinium — comprises colorless crystalline substances that dissolve well in water and alcohol, the solutions of which have surfactant (detergent) properties.

Example 1.

5-Lauryl-1-methylimidazo[4,5-*c*]pyridinium bromide (I), EYu-196.

A quantity of 10 mmol of 1-methylimidazo[4,5-*c*]pyridine is dissolved in 15 mL of absolute benzene, 12.5 mmol of dodecylbromide is added, and [the resulting solution] is boiled for 2.5 hr on an oil bath at a temperature of 110°C. After cooling, the precipitate is filtered off and recrystallized from nitromethane. Yield is 82%, and m.p. is 63–64°C (nitromethane).

Found: 59.48%, H 8.51%, N 10.9%, Br 20.7%.

$C_{19}H_{32}BrN_3$

Calculated: C 59.67%, H 8.43%, N 10.98%, Br 20.89%.

UV spectrum: λ_{max}, nm (log ε) 216 (422), 240 (3.20), 266 (3.42).

Example 2.

4-Amino-5-lauryl-1,3-dimethylimidazo[4,5-*c*]pyridinium-2-one bromide (II), KhYu-2.

A solution of 1 mmol of 4-amino-1,3-dimethylimidazo[4,5-*c*]pyridin-2-one in 0.5 mL of sulfolane and 1.2–1.25 mmol dodecylbromide is heated at 160–170°C on an oil bath for 1 hr, the reaction mass is cooled, and the precipitate is filtered off, washed with benzene and ether, and dried. Yield is 0.32 g (73%). M.p. is 134–135°C (alcohol with ether).

Found: C 55.7%, H 7.9%, Br 19.1%.

$C_{20}H_{35}BrN$.

Calculated: C 56.2%, H 8.2%, Br 18.7%.

Infrared spectrum: 3380 cm^{-1} (NH), 1730 cm^{-1} (CO).

UV spectrum: λ_{max}, nm (log ε) 222 (455):260(3.85), 292 (3.62).

The activity of quaternary salts of imidazo[4,5-*c*]pyridinium EYu-196 and KhYu-2 on the antimicrobial and fungistatic activity of compounds was studied by the method of doubling serial dilutions on a liquid medium over a range that included up to five strains of microorganisms. Hottinger broth (*p*H 7.2–7.4) was used to culture the bacteria. The microbial load for the bacteria was 2.5×10^5 cells of an 18-hr agar culture in 1 mL of medium. The highest concentration tested was 200 μg/mL.

Sabouraud's medium (*p*H 6.0–6.8) was used to grow the fungi. The load was 500,000 reproductive bodies per milliliter. The highest tested concentration was 200 μg/mL.

The antimicrobial activity of the compounds was judged by the minimum bacteriostatic and fungistatic concentration of the chemical compounds, expressed in μg/mL.

Furacilin was taken as the reference.

As one sees from the data, the drugs tested have more potent action toward staphylococcus by a factor of 2 (EYu-196), toward anthracoid by factors of 16 and 4 (EYu-196 and KhYu-2, respectively), toward colon bacillus by factors of 16 and 2, and toward *Candida abb* by factors of 16 and 4. With regard to *Bacillus pyocyaneus*, both drugs act at the standard level.

Test Results for Antimicrobial and Fungistatic Activity
(the Minimum Bacteriostatic Concentration
Is Specified in μg/mL)

No.	Strains of microorganisms and fungi	Designators of tested compounds		
		EYu-196	KhYu-2	Furacilin
1	*Staphylococcus aureus* 209p	2	8	4
2	*Bacillus anthracoides* 1312	2	8	31
3	*Escherichia coli* 675	1	8	16
4	*Pseudomonas aureginosa* 165	250	250	250
5	*Candida albicans*	4	16	63

Editor: N. Sil'nyagina Technical editor: M. Didyk Proofreader: O. Kravtsova

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(51)4 C 07 D 471/04; A 01 N 43/50

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DESCRIPTION OF AN INVENTION
FOR AN AUTHORSHIP CERTIFICATE

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(22) October 26, 1979

(46) December 23, 1986, Bulletin No. 47

(71) Institute of Physicoorganic Chemistry and Coal Chemistry of the Ukrainian SSR Academy of Sciences, and All-Union Scientific Research Institute of Plant-Protection Chemicals

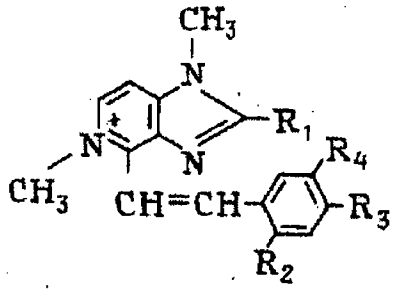
(72) Yu. M. Yutilov, A. G. Ignatenko, L. Ye. Mikhailova, Ye. I. Andreyeva, and G. V. Bobkova

(53) 547.859 (088.8)

(56) U.S. Patent No. 3,759,933, classification C 07 d 31/40, published 1973.

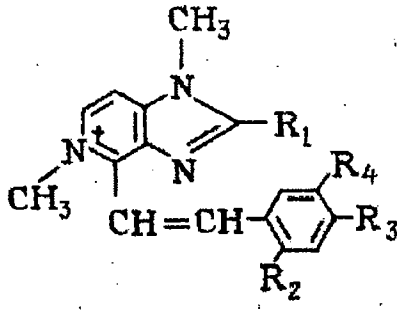
(54) STYRYL DERIVATIVES OF IMIDAZO[4,5-*c*]PYRIDINIUM EXHIBITING FUNGICIDAL ACTIVITY

(57) Styryl derivatives of imidazo[4,5-*c*]pyridinium iodide having the general formula:



where a) R_1 is CH_3, R_2 and R_3 are OCH_3, and R^3 is H;
b) R_1 is CH_3, R_2 and R_3 are H, and R_3 is $N(CH_3)_2$;
c) R_1 is CH_3, R_2 and R_4 are H, and R_3 is OCH_3;
d) R_1 is Ph, R_2 and R_4 is OCH_3, and R_3 is H; and
e) R_1 is Ph, R_2 and R_4 are H, and R is $N(CH_3)_2$,
which exhibit fungicidal activity.

The invention relates to new chemical compounds, to styryl derivatives of imidazo[4,5-*c*]-pyridinium iodide having the general formula:



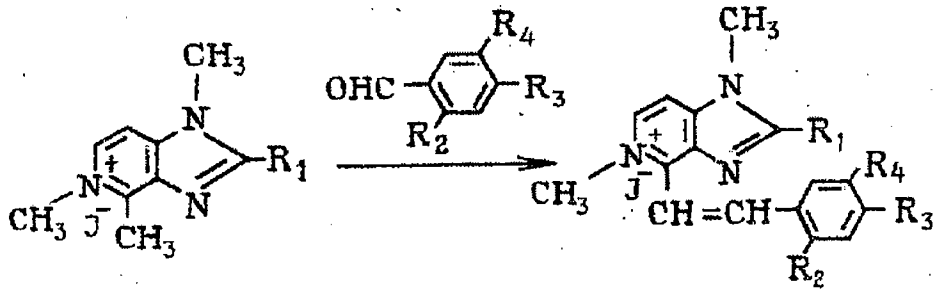
where a) R_1 is CH_3, R_2 and R_3 are OCH_3, and R_3 is H;
b) R_1 is CH_3, R_2 and R_3 are H, and R_3 is $N(CH_3)_2$;
c) R_1 is CH_3, R_2 and R_4 is H, and R_3 is OCH_3;
d) R_1 is Ph, R_2 and R_4 is OCH_3, and R_3 is H; and
e) R_1 is Ph, R_2 and R_4 are H, and R is $N(CH_3)_2$,
which have fungicidal activity.

This property makes it possible to propose the possibility that they can be used in agriculture.

Derivatives of imidazo[4,5-*c*]-pyridin-2-one exhibiting anti-inflammatory activity are known.

The object of the invention is to expand the range of fungicides.

This object is attained by new styryl imidazo[4,5-*c*]-pyridinium iodides having the cited general formula, which are obtained by reacting 4-methyl derivatives of imidazo[4,5-*c*]-pyridinium iodides with aromatic aldehydes in the presence of piperidine as a catalyst, by the following scheme:



where R_1–R_4 have the indicated meanings.

The new compounds obtained are colored solids that are soluble in water, alcohol, and acetone. The structure is confirmed by data of ultimate analysis.

Example 1. 1,2,5-Trimethyl-4-(*n'*-N',N'-dimethylaminostyryl)-imidazo-[4,5-*c*]-pyridinium iodide (IYu-6).

A quantity of 1.05 g (3.5×10^{-3} mol) of 1,2,4,5-tetramethylimidazo[4,5-*c*]pyridinium iodide and 0.7 g (4.5 mmol) of *n*-(dimethylamino)benzaldehyde are dissolved, while being heated, in 30 mL of *n*-butanol, 2 mL (2 mmol) of piperidine is added, and [the resulting mixture] is boiled on an oil bath at a temperature of 135–145°C for 2 hr. After cooling, the brick-red precipitate is filtered off and washed with ether; yield is 1.45 g (96.7%), and m.p. is 228–230°C (*n*-butanol).

Found: C 52.5%, H 5.4%, N 12.7%.

$C_{19}H_{23}N_4$.

Calculated: C 52.5%, H 5.3%, N 12.9%.

Example 2. 1,2,5-Trimethyl-4-(2,5-dimethoxystyryl)imidazo[4,5-*c*]pyridinium iodide (IYu-5).

[This compound] is obtained by analogy with Example 1, by proceeding from 1.05 g (3.5 mmol) of 1,2,4,5-tetramethylimidazo[4,5-*c*]pyridinium iodide and 0.7 [g] (4.2 mmol) of 2,5-dimethoxybenzaldehyde; yield is 1.5 g (96%), and m.p. is 184–185°C (*n*-butanol).

Found: C 50.5%, H 5.5%, N 9.2%.

$C_{19}H_{22}N_3O_2I$.

Calculated: C 50.5%, H 5.6%, N 9.3%.

Example 3. 1,2,5-Trimethyl-4-(*n'*-methoxystyryl)imidazo[4,5-*c*]pyridinium iodide (IYu-452).

[This compound] is obtained by analogy with Example 1, by proceeding from 1.05 g (3.5 mmol) of 1,2,4,5-tetramethylimidazo[4,5-*c*]pyridinium iodide and 0.51 mL (4.2 mmol) of *n*-2,5-methoxybenzaldehyde; yield is 0.96 g (63.3%), and m.p. is 235–236°C (H_2O).

Found: N 10.5%.

$C_{18}H_{20}N_3OI$.

Calculated: N 10.0%.

Example 4. 1,5-Dimethyl-2-phenyl-(2,5-dimethoxystyryl)imidazo[4,5-*c*]pyridinium iodide (IYu-428).

[This compound] is obtained by analogy with Example 1, by proceeding from 0.8 g (2.2 mmol) of 1,4,5-trimethyl-2-phenylimidazo[4,5-*c*]pyridinium iodide and 0.546 g (3.3 mmol) of 2,5-dimethoxybenzaldehyde; yield is 0.85 g (71.2%), and m.p. is 233–234°C (*n*-butanol).

Found: N 8.3%.

$C_{24}H_{14}N_3O_2I$.

Calculated: N 8.2%.

Example 5. 1,5-Dimethyl-2-phenyl-4-*n*-N′,N′-dimethylaminostyryl)imidazo[4,5-*c*]pyridinium iodide (IYu-431).

[This compound] is obtained by analogy with Example 1, by proceeding from 0.8 g (2.2 mmol) of 1,4,5-trimethyl-2-phenylimidazo[4,5-*c*]pyridinium iodide and 0.448 g (3 mmol) of *n*-N,N-dimethylaminobenzaldehyde; yield is 0.85 g (78.2%), and m.p. is 265–266°C (*n*-butanol).

Found: C 57.7%, H 5.2%.

$C_{24}H_{25}N_4I$.

Calculated: C 58.0%, H 5.1%.

Fungicidal activity was determined in the mycelium of fungi: *Botrytis cinerea*, *Fusarium moniliforme*, *Venturia inaegualis*, *Aspergillus niger*, and *Verticillium dahlick*,* and in the bacterium *Xanthomonas malvacearum*.

The new substances are dissolved in acetone and introduced, under sterile conditions, into liquefied agar, which is poured into Petri dishes. Tetramethylthiuramdisulfide (TMTD) is taken as the reference. The concentration of the active ingredient is 0.003%. Some 18–20 hr after pouring and solidification, the agar slab is inoculated with pieces of mycelium and the aforementioned test objects, and is held for 4–5 days at a temperature of 22–25°C. At the end of this period, the size of the colonies of the fungi studied is determined, and then Abbott's formula is used to determine the percent suppression (P) of the fungal mycelium in comparison with the reference:

$$P = \frac{a-c}{a} \times 100,$$

where a is the growth of the fungal mycelium in the control, and c is the growth of the fungal mycelium on the preparation.

The test results are presented in the table.

In terms of fungicidal activity, the compounds bearing identifiers IYu-452, IYu-428, IYu-5, and IYu-6 surpass or are equivalent to the reference TMTD on mycelium of the fungus *Verticillium dahlial*. The compounds IYu-6 and IYu-452 also exhibit pronounced bactericidal activity. The compound IYu-5 has activity toward the pathogen of gray mold. In addition to high fungicidal activity, the substances being filed for exhibit high selectivity of action toward fungal diseases, and this in turn protects the environment from pollution due to excessive use of chemicals as means of controlling parasitic organisms.

---

*Translator's note: In the Russian authorship certificate this species name is given in two spellings: *Verticillium dahlick* and *Verticillium dahlial*. Both spellings are used in this translation to match the original text.

Test Results for Fungicidal Activity
(The Compounds Were Tested at a Concentration of 0.003%,
Referred to the Active Ingredient)

Identifiers of compounds	*Xanthomonas malvacearum*	*Botrytis cinerra* [*sic*]	*Fusarium moniliforme*	*Venturia inaegualis*	*Aspergillus niger*	*Verticillium dahlial*
IYu-452	75	36	22	25	8	92
IYu-431	12	68	11	6	17	—
IYu-428	12	18	33	25	17	83
IYu-5	50	100	4	14	13	100
IYu-6	100	63	0	31	13	100
TMTD	87	100	100	100	87	83

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(46) Date of publication: May 27, 1998

(56) References: 1. Z. Talik and B. Brekiess, "Some pyridotriazoles and imidazoles," *Roczn. Chem.*, 1964, 38(5), p. 887, cited after *Chem. Abs.*, 62, p. 5271. 2. Yu. M. Yutilov, K. M. Khabarov, and I. A. Svertilova, Deposit No. 4182-79, 1979.

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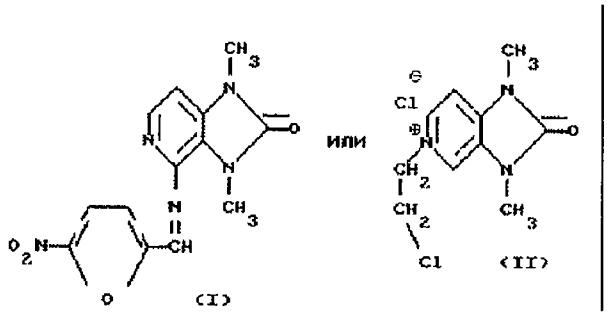
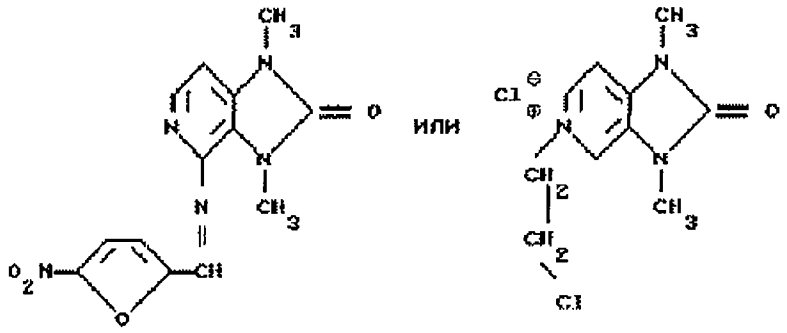
(54) DERIVATIVES OF 4-AMINO-1,3-DIMETHYLIMIDAZO[4,5-*c*]PYRIDIN-2-ONE EXHIBITING ACARICIDAL ACTION

(57) Derivatives of 4-amino-1,3-dimethylimidazo[4,5-*c*]pyridin-2-one having the formula:



which exhibit acaricidal action.

New derivatives of 4-amino-1,3-dimethylimidazo[4,5-*c*]pyridin-2-one having formula I or II are proposed:

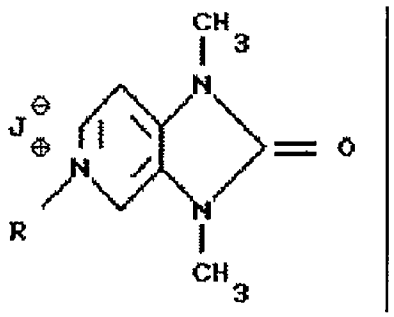


(I) (II)

which exhibit acaricidal action.

4-Hydrazinoimidazo[4,5-*c*]pyridine, which exhibits hypotensive activity [1], is known.

Also known are quaternary salts of 1,3-dimethyl-4-aminoimidazo[4,5-*c*]pyridin-2-one [2] having the general formula



where R is an alkyl, benzyl, or allyl.

However, the literature contains no data on the activity of these compounds.

The object of the invention is to expand the variety of chemical compounds that act on the living organism.

The stated object is attained by derivatives of 1,3-dimethyl-4-aminoimidazo[4,5-*c*]pyridin-2-one having formulas I and II, which exhibit acaricidal action.

Compound I is obtained by reacting 4-amino-1,3-dimethylimidazo[4,5-*c*]pyridin-2-one with 5-nitrofurfurol in alcohol while it is being boiled.

Compound II is obtained by reacting 4-amino-1,3-dimethylimidazo[4,5-*c*]pyridin-2-one with ethylene chlorohydrin at 170–180°C, followed by treatment with thionyl chloride in chloroform at 50–60°C.

Example 1.

4-(5-Nitrofurfurylidene-2-amino)-1-3-dimethylimidazo[4,5-*c*]pyridin-2-one (I).

A quantity of 0.8 g of 4-amino-1,3-dimethylimidazo[4,5-*c*]pyridin-2-one and 0.65 g of 5-nitrofurfurol are boiled in alcohol for 1 hr and cooled, and the precipitate is filtered off and dried. Yield is 1.12 g, and m.p. is 238–240°C (from ethanol).

Found: C 51.52%, H 4.01%.

$C_{13}H_{11}N_5O_4$.

Calculated: 51.82%, H 3.68%.

Example 2.

4-Amino-5-(2′-chloroethyl)-1,3-dimethylimidazo[4,5-*c*]pyridinium-2-one (II) chloride.

A quantity of 0.99 g of 4-amino-1,3-dimethylimidazo[4,5-*c*]pyridin-2-one in 1.5 mL of ethylene chlorohydrin is heated at 170–180°C for 1 hr, the ethylene chlorohydrin is driven off, 10 mL of dry chloroform and 0.5 mL of thionyl chloride are added, and [the resulting mixture] is heated at 50–60°C for 40 min and cooled, and the precipitate is washed with acetone and dried. Yield is 1.162 g, and m.p. is 172–173°C (from ethanol).

Found: C 42.88%, H 5.19%, Cl 25.93%, N 19.79%.

$C_{10}H_{14}Cl_2N_4O$.

Calculated: C 43.32%, H 5.05%, Cl 25.60%, N 20.22%.

Infrared spectrum: 3465 and 3265 cm^{-1} (ν_{NH_2}), 1705 cm^{-1} ($\nu_{C=O}$).

The compounds obtained are tested on beans for acaricidal activity in the two-spotted spider mite (*Tetranychus urticae* Koch).

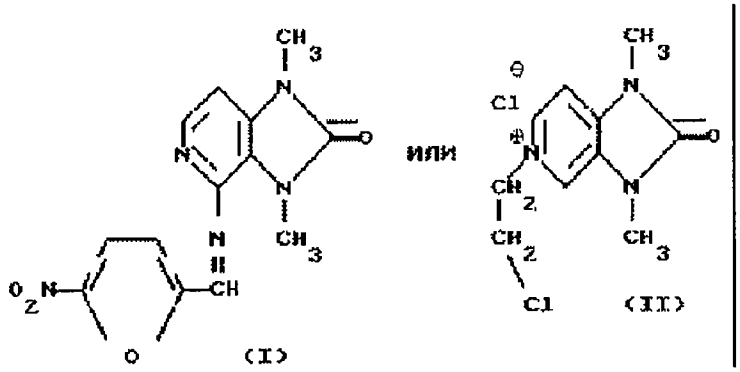
Standard cuttings from bean leaves with adult two-spotted spider mites placed on them are sprinkled with 2.5 mL of a water–acetone solution of the test compound at a concentration of 0.1% active ingredient. After the moisture in liquid drops dries away, the cuttings with the treated mites are placed in a wet chamber. The mortality of the mites is calculated after 48 hr.

Data on the acaricidal activity of the compounds tested are presented in the table.

Thus, the proposed compounds exhibit acaricidal activity and may find broad application in agricultural pest control.

Claim

Derivatives of 4-amino-1,3-dimethylimidazo[4,5-*c*]pyridin-2-one having the formula



which exhibit acaricidal action.

Compound	Mortality (%) of mites from a concentration of 0.1% referred to the active ingredient
4-Amino-5-(2′-chloroethyl)-1,3-dimethylimidazo[4,5-*c*]pyridinium-2-one chloride	84
4-(5-Nitrofurfurylidene-2-amino)-1,3-dimethylimidazo[4,5-*c*]pyridin-2-one	85
Reference: Kelthane	100